Repetitive and outpatient infusions of levosimendan to treat advanced heart failure.Clinical case review and presentation

Ciclos ambulatorios y repetitivos de levosimendán en insuficiencia cardíaca avanzada. Revisión y presentación de casos clínicos

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ABSTRACT

Advanced heart failure is defined as a clinical condition characterized by persistent symptoms (NYHA FC III-IV) despite the optimal medical therapy including cardiac resynchronization therapy, when indicated, in patients with severe ventricular dysfunction. The prognosis of these patients is poor, and the mortality rate and the rate of rehospitalizations are both high.
Recently, a new drug has been proposed for this stage of the disease: levosimendan. The intermittent infusions of levosimendan brought different clinical benefits to these patients including improved cardiac biomarkers, symptoms, quality of life, lower hospitalization rates, and lower heart failure-induced mortality rates.

Keywords: *heart failure, advanced heart failure, levosimendan.*

RESUMEN

Se define como insuficiencia cardíaca avanzada al cuadro clínico caracterizado por la persistencia de síntomas en CF III-IV (NYHA) a pesar del tratamiento médico óptimo, incluida la terapia de resincronización cardíaca, cuando está indicada, en un paciente con deterioro grave de la función ventricular. Son pacientes con elevada mortalidad y alta tasa de reinternaciones1.
En el último tiempo se ha propuesto una nueva droga para este estadio de la enfermedad: el levosimendán. Las infusiones intermitentes de levosimendán demostraron varios beneficios clínicos en estos pacientes, como la mejora de los biomarcadores cardíacos, los síntomas, la calidad de vida, las tasas de rehospitalización y la reducción de la mortalidad relacionada con la insuficiencia cardíaca.

Palabras clave: *insuficiencia cardíaca avanzada, levosimendán.*

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INTRODUCTION

Advanced heart failure is an interesting topic of discussion today because its incidence rate just does not stop growing, in part, due to the aging of the population, the higher survival regarding the patients' comorbidities, and the advances made over the last few years in new therapies. Also, it has become a common reason for consultation in the coronary units of our country and abroad[1]. As a matter of fact, it has become a huge problem for the public healthcare systems because of the high budget required. But, also a problem for the patients because of the numerous and prolonged hospital stays required to treat the symptoms, and because it deteriorates the quality of life of terminally ill patients significantly[2,3].
Over the last few years, a new and promising drug to treat advanced heart failure has come up: levosimendan. This drug has had promising results for the management of acute decompensations. Currently, the intermittent and outpatient administration of this inotropic drug has been proposed to treat patients with advanced heart failure because it reduces the number of rehospitalizations and improves the quality of life of patients with these characteristics. Also, it is a safe and cost-effective drug for the healthcare system[4].The objective of this review article is to answer the following questions based on the data already published to this date:
Is levosimendan a safe drug for an intermittent use in these patients? Is it effective and efficient? Is it economically feasible? How often should the cycles be administered? What adverse events does it cause? What is its mechanism of action? What clinical trials have tested its utility in this type of patients?

MATERIAL AND METHODS

Randomized clinical trials, medical bibliographic databases, original articles, and consensus documents published in international journals were consulted. The searches were conducted in PubMed (the United States National Library of Medicine database). Also, a non-indexed citation was included [like the consensus documents published by the Argentine Society of Cardiology (SAC)] as the experience gained in our field was deemed necessary.
The following terms, whether isolated or in combination, were used to limit the searches: "advanced heart failure", "intermittent use of levosimendan", "treatment of chronic heart failure", "levosimendan", and "outpatient inotrope infusions".
After choosing the bibliographic material that would be used, it was classified by date and relevance. All those articles published in journals with the highest impact factor, and reports published in both Spanish and English were included. Low-impact journals with insu-

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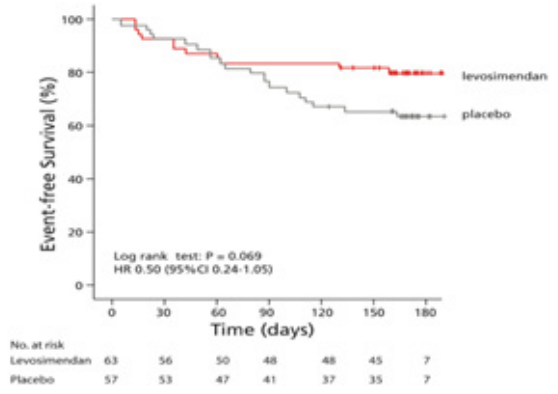

Figure 1. *Event-free survival rate at the 24-week follow-up. It shows the Kaplan-Meier curves for a secondary composite endpoint of absence of death, heart transplant or acute heart failure within the first 180 days after randomization (according to the intention-to-treat analysis) HR: hazard ratio. 95%CI: 95% confidence interval.*

fficient numbers of patients recruited (case report) were excluded. Articles published in languages different that the ones already mentioned were excluded too.

LEVOSIMENDAN

Mechanism of action

Levosimendan is an active enantiomeric drug of simendan, a pyridazinone-dinitrile derivative. For it to actually work, the action of levosimendan and its active metabolite OR-1896 are both required. Its main 3 mechanisms of action are: positive inotropism (this agent sensitizes troponin C to calcium in a manner dependent on the calcium concentration in the contraction-relaxation mechanism); vasodilation, and cardioprotective effect against ischemia and myocardial damage induced by ischemia-reperfusion thanks to its contribution opening the mitochondrial membrane-dependent ATP-sensitive potassium channels.

Its half-life is one of its most significant features: 1 h to 1.5 h for levosimendan, and approximately 80 h for its active metabolite. This means that its effects can still be seen almost 1 week after withdrawing the IV infusion, making it an attractive drug for patients with advanced heart failure. Regarding the drug washout in cases of patients with severe kidney or liver failure, only the prolonged washout of the OR-1896 metabolite has been described, and no pharmacological or hemodynamic changes have been reported to this date[5].

Posology

The patients who are eligible to receive intermittent infusions of levosimendan are those with a diagnosis of advanced heart failure with NYHA functional class (FC) III-IV, and an ejection fraction (EF) < 35%. Also, patients with recurring hospitalizations due to heart failure within the last year. Also, all of the above should have happened despite the optimal medical therapy too. Ineligible patients are those with a past medical history of drug intolerance, a diagnosis of severe LVOT obstruction, severe uncorrected valvular heart disease with significant hemodynamic compromise or SAP < 90 mmHg.

Although the early bolus of a loading dose has proven useful in cases of acute decompensated heart failure, it was found that in patients with advanced heart failure this strategy predisposes to a higher rate of adverse events since, in general, these patients are less tolerant to this drug due to their baseline hemodynamic status. Therefore, it is thought that the bolus of levosimendan should only be administered if immediate effects are sought and systolic arterial pressure exceeds 100 mmHg.

Therefore, the early dose will depend on the characteristics and needs of each particular patient. An early low dose of 0.1 μg/kg/min is advised that could be gradually up titrated to 0.2 μg/kg/min if tolerated. If it not tolerated, it can be reduced to 0.05 μg/kg/min and see what happens next. If not tolerated either, then the infusion should be withdrawn. Each infusion consists of a continuous 24-h IV infusion that should be repeated every 2 to 4 weeks[6-8].

Intrainfusion monitoring

Prior to the infusion it is recommended to keep arterial hypertension, heart rate, body weight, and the serum levels of sodium and potassium, and creatinine under control.

The patient's volume status should be carefully assessed since in cases of hypovolemia, fluid replenish fluids may be required during the infusion of levosimendan. In the presence of hypotension (SAP < 90 mmHg), it may be necessary to reduce the dose of levosimendan and/or add a vasopressor temporarily (such as noradrenaline).

In some patients increased diuresis can be seen as a result of treatment with levosimendan. Therefore, eliminating or reducing the routine diuretic on the day of the treatment and administering additional fluids should be considered, when appropriate. The assessment of renal function is relevant in patients with known kidney failure as well as in those on diuretic therapy. Although secondary kidney dysfunction is not a contraindication to treatment with levosimendan, we need to be very cautious about it. Given the specific nature of the progression of chronic advanced HF no general recommendations have been made on the threshold of glomerular filtration rate (GFR) regarding the repeated use of levosimendan; however, GFRs = 30 mL/min could be regarded as a safety threshold. If furosemide is coadministered simultaneously, the doses of the diuretic should be adjusted on the same day of levosimendan infusion[9].

Adverse events

Although levosimendan is a drug well-tolerated by most patients with heart failure, adverse events like arterial hypotension, headache, and dizziness due to its vasodilator effect can occur. Also, a higher rate of atrial fibrillation and ventricular tachycardia has been reported in most studies. Although fewer arrhythmias have been reported in clinical trials that compared levosimendan and dobutamine to placebo, ventricular tachycardia (25% vs 17%) and atrial fibrillation (8% vs 2%) were more common in the levosimendan group compared to the standard therapy group in the REVIVE II and other clinical trials; in the SURVIVE trial, atrial fibrillation (9.1% vs 6.1%), and ventricular tachycardia (7.9% vs 7.3%) were more common in the levosimendan group compared to the dobutamine group.

Regarding the lab parameters, some studies have described a slight decrease of red blood cell counts, hematocrit, and hemoglobin levels (10%), and, especially in patients who were getting high doses, a slight decrease of the serum levels of potassium has been reported. Serum creatinine levels were reduced even in patients with baseline renal dysfunction[10].

In general, the studies have proven that levosimendan does not deteriorate or trigger myocardial ischemia. However, the excessive reductions of arterial blood pressure can reduce the coronary perfusion pressure and even cause ischemia in some cases[11,12].

Cost-effectiveness

Heart failure is the leading cause of hospitalization in patients > 65 in developed countries. It is a progressive fatal disorder despite the optimal medical therapy.

Over the last few decades, the prevalence and hospitalizations due to heart failure have increased significantly in developed countries. This is mainly due to the growing number of old people across the world, the arrival of new therapies, and much better control of mortality and morbidity. That is how the survival rate of patients with acute myocardial infarction has increased. In addition, this higher survival rate has also increased the possibilities of developing heart failure[13].

Also, there is evidence that the best therapies against heart failure (angiotensin-converting enzyme inhibitors [ACEI], beta-blockers, neprilysin inhibitors [sacubitril-valsartan], and the newly arrived gliflozins) are having an impact on the population by improving the survival rate of patients with heart failure. Therefore, the population increasing survival rate is associated with a higher prevalence of heart failure[14].

Heart failure, especially in advanced stages, is associated with numerous hospitalizations posing a tremendous problem for public healthcare regarding costs (whether direct or indirect).

Direct costs include hospital services, healthcare workers, medications, devices, as well as outpatient and home care, and the follow-up patients may need.

Indirect costs include the loss of productivity as a result of the patient's morbidity and mortality, sick pays, and social care. There are data available on the economic impact of heart failure in 197 countries. Back in 2012 the overall annual cost attributed to heart failure were $108 billion. Of these, 60% corresponded to direct costs, and the remaining 40% to indirect costs.

For all this, the outpatient cycles of levosimendan in this type of patients are very interesting because they would reduce the number of hospitalizations saving costs for the entire healthcare system[15].

Based on the results seen in the LION HEART trial, the patients randomized to the levosimendan group experienced a significant drop in the rate of hospitalization due to heart failure (hazard ratio [HR], 0.25; 95% confidence interval [95%CI], 0.11-0.56; P = .001) compared to those who received placebo. Also, this improved rate of heart failure-induced hospitalizations translated into significant reductions of cardiovascular hospitalizations, all-cause hospitalizations, and fewer combined assessment criteria between hospitalization (all-cause, cardiovascular etiology or heart failure) and death or other end-stage events.

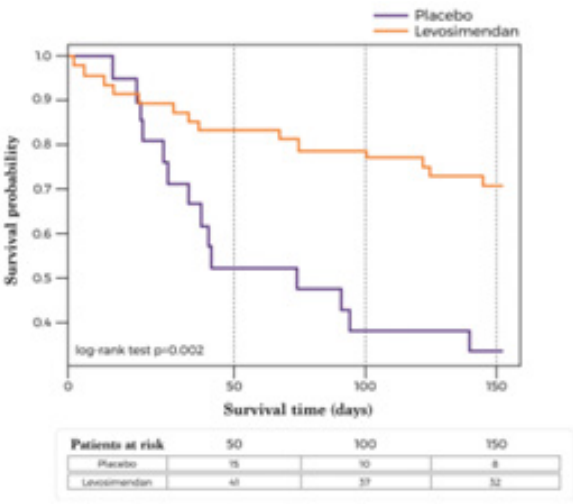

Figure 2. *Kaplan-Meier survival curves (time until the first event) for the composite endpoint of all-cause mortality or hospitalizations due to heart failure.*

Back in 2020, *Revista Española de Cardiología* published an article entitled "Economic analysis of intermittent intravenous outpatient treatment with levosimendan in advanced heart failure in Spain" (English translation from the Spanish original title "Análisis económico del tratamiento ambulatorio intermitente con levosimendán de la insuficiencia cardíaca avanzada en España". This article confirmed that nearly €700 per patient/month could be saved using outpatient cycles of levosimendan with the plan proposed in the LION HEART trial (6 cycles total) in patients with advanced heart failure. In conclusion, the chances that money would be saved with levosimendan compared to the option of not treating at all would be somewhere around 94.8%.[16]

Thus, the outpatient and repetitive cycles of levosimendan in patients with advanced heart failure not only improve the patients' quality of life but also reduce the number of rehospitalizations and the corresponding healthcare costs. Therefore, this plan is both effective as well as it is efficient[17].

OUTPATIENT CYCLES OF LEVOSIMENDAN TO TREAT ADVANCED HEART FAILURE: CURRENT EVIDENCE

Up until now, 3 studies have been published showing the benefits of this drug in patients with stage D heart failure. One of these studies is the LAICA trial. This Spanish, randomized, multicenter, double-blind, prospective, placebo controlled Spanish trial published in 2013 included patients with advanced heart failure of any etiology with, at least, 1 episode of decompensation requiring hospitalization over the last 6 months but still stable when entering the study. The study duration was 24 months total, 12 months of treatment, and 12 months of follow-up. All patients received the same standard therapy to treat their heart failure. The patients eligible to be treated with levosimendan received a dose of 0.1 µg/kg/min without loading dose for 24 hours once every 30 days.

The study primary endpoint was to determine the composite event rate of all-cause mortality and hospitaliza-

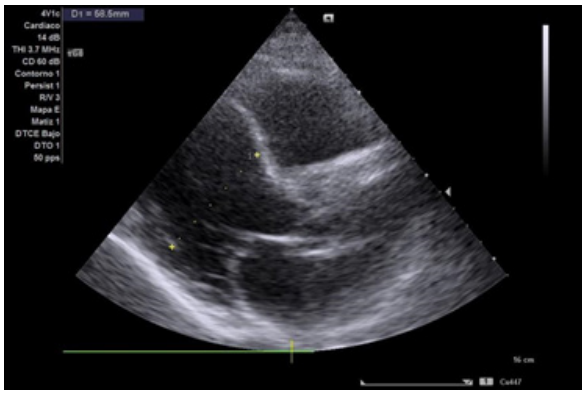

Figure 3. *Doppler echocardiography. Presence of left ventricular dilatation. Severe estimated EF <20%.*

tions or worsening of the heart failure symptoms. The study secondary endpoints were time from the administration of treatment until the next hospitalization, mortality at 1, 6, and 12 months, FC changes according to the NYHA, changes in the proBNP levels before and after treatment, and quality of life measured using the KCCQ at 1, 6, and 12 months.

Although the study had to be interrupted because it did not reach the 261 patient-mark required, which was the sample size needed to verify the hypothesis, 97 patients were eventually analyzed. The results obtained were encouraging. Regarding the rate of rehospitalizations due to acute decompensation in patients treated with levosimendan, it was found that the percentage of patients who were being rehospitalized was lower. However, we should mention that there was a statistically significant difference between the 2 groups within the 3 first months of treatment. Sometime later, although the difference in the rate of hospitalization due to acute decompensation still remained, this rate stopped being statistically significant. The same thing was seen in the analysis of the patients' mortality[18].

Another important study is the LevoRep trial. It was a randomized, multicenter, double-blind, prospective, placebo controlled trial published in 2014 that included a total of 120 patients randomized into 2 groups: 63 into the levosimendan group, and 57 into the placebo group. All patients had been diagnosed with advanced heart failure, at least, 3 months before entering the study (NYHA FC III-IV), had an EF ≤ 35%, and 6-minute walk test results < 350 m while on standard neurohormonal treatment. The exclusion criteria were SAP ≤ 100 mmHg, serum potassium levels < 3.5 mmol/L or > 5.5 mmol/L, and creatinine clearance levels < 30 mL/kg/m^2.

It was a 2-stage study. The first stage was the administration of a 6-month course of treatment where patients received a total of 4 cycles of levosimendan with doses of 0.2 μg/kg/min (without loading doses) for 6 hours every 2 weeks followed by an 18-month medical follow-up.

The study primary composite endpoint was a > 20% improvement in the 6-minute walking test and an increase of, at least, 15% in the KCCQ score at 24 weeks. The study secondary endpoint was the "event-free" state in the short and long-term (8 and 24 weeks, respectively). The percentage of patients who meet the study primary composite endpoint at the 24-week follow-up was not statistically significant between the levosimendan group (19%) and the placebo group (15.8%) (odds ratio [OR], 1.25; 95%CI, 0.44-3.59; P = .810). Similarly, no differences were seen between the groups after 8 weeks (OR, 1.17; 95%CI, 0.48-3.02; P = .823).

Regarding the study secondary endpoint, after 24 weeks, 11 patients from the levosimendan group (17.4%) and 20 patients from the placebo group (35.1%) were analyzed. One patient from the former group died (1.6%), another patient received a heart transplant (1.6%), and 9 experienced heart failure decompensations (14.2%) compared to the placebo group with 4 (7%), 2 (3.5%), 14 (24.5%) patients, respectively.

Therefore, although this study did not show significant differences in its primary endpoint, it actually did so in its secondary endpoint showing fewer cardiovascular deaths, decompensations due to CHF, and need for a heart transplant after 24 weeks[19].

Finally, we have the LION-HEART, a multicenter, double-blind, randomized, and placebo controlled trial published back in 2018 that included 69 patients. A total of 48 of these patients were randomized into the levosimendan group and 21 into the placebo group. The main inclusion criteria were age > 18 years, EF < 35%, and a clinical diagnosis of advanced heart failure.

Patients from the levosimendan group received a 6-hour IV infusion (0.2 μg/kg/min without bolus) every 2 weeks for 12 weeks (6 cycles) with a mean total cumulative dose of 31.5 mg. The study primary endpoint was the effect on the serum concentrations of the N-terminal pro B-type natriuretic peptide (NT-proBNP) during the entire period of treatment compared to placebo. The study secondary endpoint included the assessment of safety, clinical events, and health-related quality of life (HRQoL). The area under the curve of the NT-proBNP levels throughout the course of treatment for patients who received levosimendan was significantly smaller compared to the placebo group (P = .003). Also, compared to the placebo group, patients treated with levosimendan experienced fewer heart failure-related hospitalizations (P = .001). Also, patients on levosimendan had fewer chances of seeing their quality of life deteriorated significantly across time (P = .02). The rate of levosimendan-related adverse events was similar in both groups of treatment.

Therefore, this small study (69 patients total) proved that the intermittent outpatient administration of levosimendan is safe and improves the levels of NT-proBNP significantly after 12 weeks of treatment. Also, the number of rehospitalizations due to heart failure dropped[20].

The RELEVANT-HF is a multicenter trial published in 2018 designed to obtain information on the efficacy and safety profile of repeated and scheduled 24-hour infusions of levosimendan infusions in patients with advanced heart failure. A total of 185 patients with NYHA functional class III-IV were included, with ≥ 2 hospitalizations due to heart failure over the last 6 months and left ventricular systolic dysfunction. These patients were treated with levosimendan in doses somewhere between 0.05 μg/kg/min and 0.2 μg/kg/min, without a previous bolus, every 3 to 4 weeks.

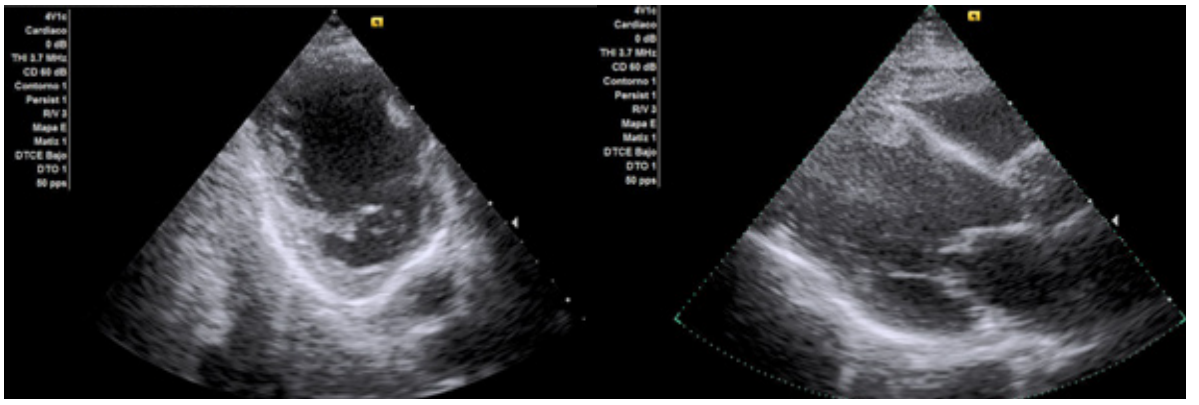

Figure 4. *Doppler echocardiography. Short axis and longitudinal axis. Presence of left ventricular dilatation with severe systolic dysfunction.*

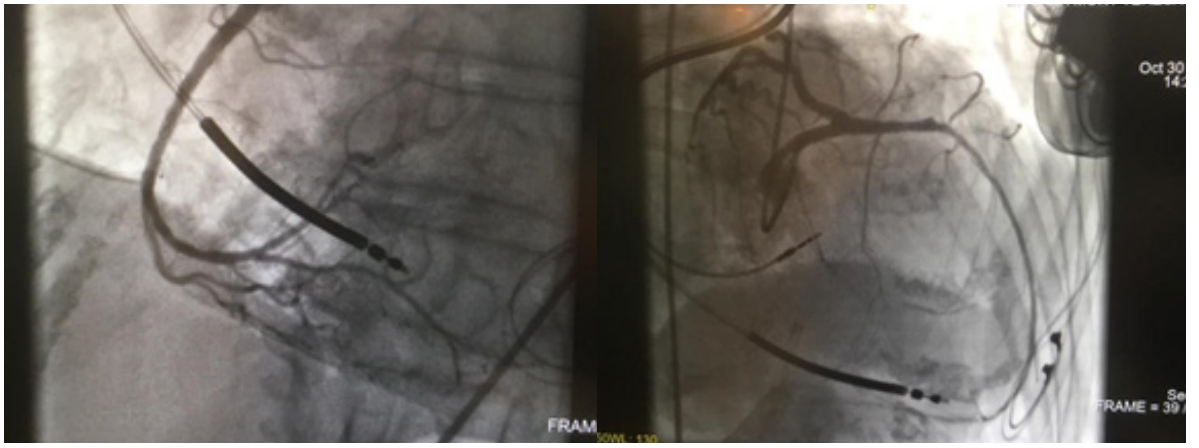

Figure 5. *Cine coronary arteriography. The image on the left shows the dominant right coronary artery with previous stent implantation at patent proximal level with collateral circulation towards the territory of the left circumflex artery. The image on the right shows a narrow-caliber left anterior descending coronary artery with stent implantation in its patent proximal third with a 30% restenosis, and a left circumflex artery occluded at 100%.*

The data on the hospitalizations due to heart failure at the 6-month follow-up before and after starting therapy were compared.

The results obtained were infusion-related adverse events occurred in 23 patients (12.4%) being the most common of all ventricular arrhythmias (16, [8.6%]). At the follow-up, 37 patients (20%) required treatment adjustments due to clinical instability (reductions in the infusion dose, infusion rate or infusion interval). The rate of hospitalization days dropped 6 months before and 6 months after treatment (9.4 [8.2%] vs 2.8 [6.6%]; $P < .0001$) as well as the duration of heart failure-related hospital stays (17.4 [15.6%] vs 21.6 [13.4%] days; $P = .0001$). Overall, the annual survival rate was 86% while 78% of the patients remained free from death, ventricular assist device or emergency heart transplant.

Nonetheless, this study is observational, meaning that the results need to be validated in randomized, double-blind, controlled clinical trials that are more accurate and reliable to assess the efficacy of drugs[21].

Currently, different studies are ongoing like the multicenter, international, double-blind, placebo controlled LeoDOR trial that will be studying the efficacy and safety profile of an intermittent therapy of levosimendan added to the optimal standard therapy in patients recently hospitalized due to heart failure decompensation. The inclusion criteria are: patients > 18 years with a diagnosis of heart failure, at least, 6 months prior to starting the study; patients on optimal medical therapy and devices implanted; LVEF ≤ 30% assessed on the echocardiography, ventriculography or contrast angiography during hospitalization; patients currently hospitalized or hospitalized within the previous 12 months due to decompensated heart failure and requiring diuretics, vasodilators or IV inotropic agents; patients with NT-proBNP levels after compensation ≥ 2500 ng/L and/or NYHA FC III-IV at the time of entering the study. The exclusion criteria are: heart surgery or coronary angioplasty within the 30 days prior to starting the study drug; acute coronary syndrome within the 30 days prior to starting the study; past medical history of torsades de pointes; systolic arterial pressure < 90 mmHg at the beginning of the study; heart rate ≥ 120 beats/min at the beginning of the study, serum potassium levels < 3.5 mmol/L; glomerular filtration rate ≤ 30 mL/min/1.73 m^2; administration of levosimendan within the 14 days prior to starting the study drug, and hypersensitivity to levosimendan, among others.

It is well-known that patients randomized to the levosimendan group can receive the drug through two different ways: as a 6-hour continuous infusion at an infusion rate of 0.2 μg/kg/min every 2 weeks (receiving the drug on days 0, 14, 28, 42, 56, 70, and 84) or as a 24-hour continuous infusion at an infusion rate of 0.1 μg/kg/min every 3 weeks (on days 0, 21, 42, and 84) with follow-ups 14 and 180 days after the first infusion.

The study primary endpoint is to compare the effects of intermittent pulses of levosimendan versus placebo in

patients with advanced chronic heart disease during a vulnerable period of 14 weeks after a recent hospitalization in a criterion of global assessment where all participants will be categorized into 3 hierarchical groups (in ascending order): time until death or emergency heart transplant or VAD implantation; time until the occurrence of a nonfatal heart failure event requiring vasoactive treatment; and time-averaged proportional change in the NT-proBNP since the beginning of treatment until the 14 week-mark.

The study secondary endpoints are the effects derived from intermittent pulses of levosimendan on each individual component of the primary assessment criterion after 14 and 26 weeks (the time-averaged proportional change in the NT-proBNP will be determined from baseline until week 14 only), the changes seen in the symptoms and functional status at the 14 week-mark, the cumulative number of episodes of acute heart failure, and the cumulative days of life out of the hospital setting after 14 and 26 weeks.

Additional study endpoints are to determine the effects that the intermittent administration of levosimendan has on the changes made to the baseline medication and the biomarkers as well as the cost-effectiveness ratio.

Estimating that a total of 264 patients will be included (6-hour infusion group: N = 88, levosimendan and N = 44, placebo; 24-hour infusion group: N = 88, levosimendan and N = 44, placebo) this study will have a simulated statistical power of ≈ 90% to detect differences between the groups of levosimendan and placebo. The Wilcoxon-Mann-Whitney test will be run at the two-sided 5% level of significance.

Although this study was intended to be completed in February 2020, it is still going, and its results are still pending publication[22].

CLINICAL CASE PRESENTATION

Clinical case #1

This is the case of a 67-year-old woman with a past medical history of dilated cardiomyopathy due to viral myocarditis during childhood, severe left ventricular systolic dysfunction (< 20%) with an ICD for primary prevention, and multiple hospitalizations due to decompensated heart failure. She was on complete medical therapy for that underlying condition and now presents with decompensated heart failure. The patient showed progressive dyspnea (FC II/III) at admission, and an increased weight of approximately 4 kg. On the physical examination, the patient showed clear signs of fluid overload. The lab results were positive: urea levels, 65 mg/dL; creatinine levels, 1.45 mg/dL; BNP levels, 2000 pg/mL, and lactate levels, 3.5 mmol/L.

Added to the symptomatic treatment started with IV loop diuretics for negative fluid balance due to signs of volume overload, the patient was administered a 24-hour cycle of levosimendan without loading dose while keeping an IV infusion of 0.2 µg/kg/min. She tolerated the cycle well and the dose was not reduced due to hypotension or other drug-related adverse events. Twenty-four hours after completing the infusion, the patient's symptoms improved significantly as well as the lab parameters of both the renal function, lactic acid, and the serum levels of BNP. The patient was discharged from the hospital 72 hours after the infusion of levosimendan.

Afterwards, it was decided to keep on administering outpatient cycles of levosimendan every 4 to 6 weeks as palliative treatment of advanced heart failure. The patient's heart failure improved after every cycle. Also, there was a significant reduction of hospitalizations due to decompensated heart failure, which eventually improved the patient's quality of life.

Clinical case #2

This is the case of a 74-year-old male patient with a past medical history of coronary artery disease (AMI at 40 years old: 3 bypass surgeries: LIMA to LAD, vein graft to CXI plus another vein graft to RCA). Severe deterioration of left ventricular systolic function (25%) of necrotic ischemic etiology treated with an ICD + resynchronization therapy in the year 2000 for primary prevention purposes. Also, chronic kidney disease (usual creatinine levels = 2.5 mg/dL to 3 mg/dL). The patient remains without the optimal medical therapy due to renal failure and intolerance. The patient presented to his GP with signs of asthenia, adynamia, a severely impaired renal function (creatinine levels = 4 mg/dL), and increased weight (5 kg) unresponsive to outpatient oral diuretics. It was decided to hospitalize the patient in the hospital coronary care unit. The physical examination showed signs of volume overload with RHY+, lower limb swelling 3/6, bilateral crakles, and no signs of low cardiac output. The only altered lab parameter was the acute exacerbation of chronic kidney disease, and BNP levels = 1890 pg/mL.

It was decided to administer IV diuretics and the continuous infusion of furosemide at 500 mg is started with good response; due to the patient's kidney disease and hemodynamic intolerance other drugs are contraindicated. The patient's dyspnea improved as well as his signs of congestion and returned to his normal creatinine levels with negative fluid balance.

Before being admitted to the hospital, it was decided to administer a 48-hour cycle of levosimendan without loading dose while keeping an infusion rate of 0.05 µg/kg/min (maximum dose tolerated). Finally, the patient was discharged with further outpatient follow-ups with his cardiologist who decided to continue with the same plan of outpatient and repeated infusions of levosimendan approximately every 8 weeks. The patient's quality of life improved although his heart failure was still in an advanced stage.

Clinical case #3

This is the case of a 79-year-old woman with a past medical history of coronary artery disease (AMI at 60; treated with primary angioplasty with 4-stent implantation (2 BMS in the LAD + 2 BMS in the RCA), ischemic-necrotic dilated cardiomyopathy, severe left ventricular systolic dysfunction (< 20%), ICD + resynchronization therapy for primary prevention, and chronic kidney disease (usual creatinine levels = 2.5 mg/dL to 3 mg/dL–on dialysis 3 times/week). The patient had been hospitalized multiple times due to heart failure. Her cardiologist had prescribed loop diuretics (80 mg/8 hours), spironolactone (12.5 mg/day), and sacubitril-valsartan (50 mg/12 hours).

The patient presented with progressive dyspnea from FC III to FC IV and an increased weight of 5 kg. The patient presented these values at admission: BP, 90/60 mmHg; HR, 60 bpm; O_2Sat, 94%, clear signs of volume overload, no clinical signs of low cardiac output, and the following lab parameters: creatinine levels of 2.7 mg/dL, BNP levels > 5000 pg/mL, and lactate levels of 3 mmol/L. Negative fluid balance is started through the continuous infusion of 500 mg of furosemide. Medication is withdrawn (sacubitril-valsartan, and aldosterone antagonists due to contraindications). The patient's hemodynamic status improved after adjusting the medication. Afterwards, a course of levosimendan was indicated at the maximum dose tolerated (0.05 μg/kg/min). The patient's symptoms improved, and she was discharged from the hospital with outpatient follow-up by her cardiologist; to this date, she is still on a 3-week dialysis plan.

Afterwards, the patient was hospitalized multiple times (at the 3-year follow-up) to alleviate her symptoms and received repetitive cycles of levosimendan in the last stage of the disease.

DISCUSSION

Levosimendan is a valid inotrope agent that can be administered intermittent and outpatiently through 24-hour infusions every 2 or 4 weeks in patients with advanced heart failure to improve symptoms and reduce the number of hospitalizations.

Although the current evidence mentioned in this review confirmed these benefits, several studies like the LION HEART (n = 69), the LAICA (n = 97), and LevoRep (n = 120) clinical trials included a rather small number of patients.

For example, the LION HEART trial was not statistically powered to assess the different clinical events, symptoms, and results reported by the patient. Given the size of the sample estimated, all assessments were planned as "exploratory". However, the findings for these secondary endpoints were consistent with the results of the criterion of global assessment and also statistically significant despite the limited size of the sample. Or else, the LAICA trial had to be suspended because the necessary 261 patients to conduct the study could not be recruited, which was the sample size estimated to verify the hypothesis. Therefore, the efficacy and safety profile of levosimendan in patients with advanced heart failure still needs further study in randomized, double-blind, clinical trials with larger recruitments of patients.

Regarding the drug cost-effectiveness ratio for this type of patients, different studies proved that this ratio is cost-effective and profitable because it reduces costs to the healthcare system by minimizing the number of hospitalizations significantly. Nonetheless, the studies focused on this issue have been conducted in developed countries where the prevalence of this condition is higher, and the economic resources destined to healthcare are different from our setting. Therefore, the cost-effectiveness ratio should be assessed in our country where two different parallel realities coexist: the public health and the private healthcare system.

CONCLUSION

The intermittent infusions of levosimendan brought several clinical benefits to patients with advanced heart failure. These infusions improved the patients' cardiac biomarkers, symptoms, quality of life, rates of re-hospitalization, and also reduced the mortality rate due to heart failure.

Levosimendan is different from any other inotrope agents (catecholaminergic drugs) thanks to its 3 mechanisms of action: positive inotropism, vasodilation, and cardioprotection. Also, its pharmacokinetics allows a prolonged action of metabolite OR-1986, thus providing additional therapeutic cardiovascular effects for days after interrupting the drug infusion, which is a huge advantage compared to other inotrope agents.

The data that back the use of levosimendan confirm that, overall, this drug is well tolerated and has few adverse events, mostly reversible, like hypotension, headache, and dizziness.

Patients diagnosed with advanced heart failure are unstable *per se*, and their decompensation starts long before being hospitalized; for this reason, the intermittent and outpatient administration of levosimendan for symptom improvement was proposed here. Also, because it improves the patients' quality of life and reduces the number of re-hospitalizations. However, further studies with more patients are still needed to assess the efficacy and effectiveness profile of levosimendan in our setting to confirm or deny the hypothesis presented in this article review.

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