

Editorial comment

Levosimendan as a bridge to heart transplant: a real alternative

Levosimendán como puente al trasplante cardiaco: una alternativa real

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Heart failure (HF) is a public health concern, affecting more than 26 million people worldwide and its prevalence is rising.¹ Although the prognosis of HF patients has greatly improved in recent years, HF-related morbidity and mortality are very high and heart transplantation (HTx) remains the treatment of choice for selected patients who develop advanced HF (aHF) despite optimal treatment. Although HTx outcomes show continual improvement, with survival reaching 76.2% in the third year after transplant, the use of treatment is limited by a shortage of donors for the ever-growing number of recipients.² The time spent by patients on the HTx waiting list varies and is influenced by parameters such as the recipient's body surface area and blood group, as well as by center-specific conditions. During this period, there is a very high risk of hospitalization for HF or cardiogenic shock.³ Consequently, the use of ventricular assist devices has been expanded as an alternative for patients with aHF. Another attractive strategy explored by several groups is the administration of inotropic agents to avoid hospital admission and improve the quality of life of patients with aHF.^{4–8}

Levosimendan is a positive inotropic agent, unique in its class, which has several mechanisms of action. On the one hand, it binds to troponin C to increase its sensitivity to calcium without increasing its intracellular concentration. This improves myocardial contraction and relaxation without elevating myocardial oxygen consumption, in contrast to other inotropic agents.^{9,10} On the other hand, levosimendan activates adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells, which induces systemic vasodilatation, an effect enhanced by selective inhibition of the intracellular phosphodiesterase III isoform.¹⁰ These effects are shared with its active metabolite OR-1896, which has a long half-life, permitting a sustained therapeutic effect for several days after a single intravenous administration of the drug.

Levosimendan has a particularly favorable profile in the field of aHF as a positive inotrope and long half-life inodilator, whose effect is not limited by the concomitant use of beta-blockers. Its intermittent administration is associated with symptomatic improvement and a significantly reduced concentration of the N-terminal pro-brain natriuretic peptide (NT-proBNP) fraction;

the drug also appears to decrease hospitalizations for HF, with a good tolerance and safety profile.^{4–6,11} These data are derived from studies with significant methodological differences, particularly the administration regimen and total doses received by the patients, which may explain the discrepancies in the results obtained. Levosimendan is widely used in HF units, and its safety and clinical benefits are supported by several clinical practice registries.^{7,12} Although the literature includes a broad spectrum of patients with aHF, the specific population of patients on the waiting list for HTx is poorly represented and the scientific evidence in this group is limited to small case series.^{8,13,14}

A study recently published in *Revista Española de Cardiología* by de Juan Bagudá et al.¹⁵ involves a Spanish multicenter registry that included 1015 patients on the waiting list for HTx and whose main objective was to describe the clinical characteristics of patients receiving levosimendan. These results represent the strongest scientific evidence published to date on the use of levosimendan in patients with aHF as a bridge to HTx. This is especially relevant and valuable in a field such as aHF, where there is a pressing clinical need and it is sometimes necessary to use measures not standardized by clinical practice guidelines.

In total, 238 patients (23.4% of the cohort) received more than 1 levosimendan dose on an outpatient basis. Compared with patients not requiring this treatment, levosimendan-treated patients had a higher risk profile. Administration patterns showed considerable heterogeneity among centers; the most frequent concerned the administration of a fixed dose of the drug at flexible intervals depending on clinical needs.

As a secondary objective, the incidence of severe adverse events was examined; the safety and good tolerability of this strategy in aHF was again demonstrated, with only 0.8% of patients developing a nonfatal ventricular arrhythmia during administration and with a very low rate of drug discontinuation due to adverse events (2.1% of patients). These results are in line with observations in studies performed outside the context of an HTx waiting list,^{4–7,12} as well as the experience of a center recently reported by Ponz de Antonio et al.,⁸ which included 11 patients with aHF on a waiting list for HTx who received twice-weekly levosimendan cycles on an outpatient basis. In all patients, drug administration was safe, with no evidence of ventricular arrhythmic events. This is of the utmost importance in this particularly vulnerable group of patients awaiting a definitive treatment such as HTx.

The authors also assessed the frequency of hospital admissions for HF. No difference was observed between the group treated with

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levosimendan from the start of the registry and the control group. However, analysis of a subgroup of patients who started treatment during follow-up, all after an admission for HF (n = 102), revealed a decrease in hospital admissions compared with the period prior to the start of levosimendan use (monthly admission rate, 0.21 vs 0.7). Similar findings were reported by Ponz de Antonio et al.⁸ This reduction in admissions for HF should be interpreted with caution because the follow-up of levosimendan-treated patients is stricter, with adjustments in the pharmacological management of HF and in diuretics during the sessions, as acknowledged by the authors in their discussion of the limitations of their study. Notably, the time on the waiting list for elective HTx was not very long (4.2 [interquartile range, 1.4–9.1] months), indicating that the results may not be completely generalizable to longer waiting list times (particularly in patients with unfavorable characteristics for early HTx).

An interesting finding was that the most frequent administration pattern in real-world clinical practice is that of fixed doses based on clinical need, similar to the findings in the national LEVO-D registry, which evaluated the use of levosimendan as destination therapy.⁷ This pattern contrasts with the protocols used in clinical trials.^{4–6} Given that the dropout rate due to clinical futility was lower among these patients (7% vs 40%), it is conceivable that flexible and personalized administration of levosimendan may be a better strategy in this situation.

Survival in levosimendan-treated patients in this registry was comparable to that of the control group and there was no difference in the need for urgent HTx according to levosimendan administration or, if received, the regimen chosen. Finally, no impact was observed on the post-HTx clinical course of levosimendan-treated patients, with no increases in the rates of primary graft failure or need for mechanical circulatory support. These data provide further support for the safety of the drug, which is maintained beyond HTx and is independent of the protocol received.

In conclusion, the study published by de Juan Bagudá et al.¹⁵ fills a gap in the literature on the intermittent use of levosimendan in patients with aHF as a bridge to HTx.¹⁵ This strategy is often applied and exhibits different management patterns among centers. Levosimendan is a safe and well-tolerated drug, even by patients with an elevated clinical risk profile, and it appears to reduce HF hospitalizations. Thus, intermittent outpatient administration of levosimendan may be an appropriate strategy to maintain clinical stability while patients await elective HTx. This may be especially relevant for patients who are not good candidates for other measures such as ventricular assistance.

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CONFLICTS OF INTEREST

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REFERENCES

1. Ambrosy AP, Fonarow GC, Butler J, et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. *J Am Coll Cardiol*. 2014;63:1123–1133.
2. González-Vílchez F, Gómez-Buena M, Almenar-Bonet L, et al. Spanish heart transplant registry. 33rd official report of the Heart Failure Association of the Spanish Society of Cardiology. *Rev Esp Cardiol*. 2022;75:923–932.
3. Barge-Caballero E, Segovia-Cubero J, Almenar-Bonet L, et al. Preoperative INTERMACS Profiles Determine Postoperative Outcomes in Critically Ill Patients Undergoing Emergency Heart Transplantation: Analysis of the Spanish National Heart Transplant Registry. *Circ Heart Fail*. 2013;6:763–772.
4. Altenberger J, Parisis JT, Costard-Jaeckle A, et al. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial. *Eur J Heart Fail*. 2014;16:898–906.
5. Comín-Colet J, Manito N, Segovia-Cubero J, et al. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial: Levosimendan in advanced HF: the LION-HEART trial. *Eur J Heart Fail*. 2018;20:1128–1136.
6. García-González MJ, Aldea Perona A, Lara Padron A, et al. Efficacy and safety of intermittent repeated levosimendan infusions in advanced heart failure patients: the LAICA study. *ESC Heart Fail*. 2021;8:4820–4831.
7. Dobarro D, Donoso-Trenado V, Solé-González E, et al. Intermittent inotropic support with levosimendan in advanced heart failure as destination therapy: The LEVO-D registry. *ESC Heart Fail*. 2023;10:1193–1204.
8. Ponz de Antonio I, de Juan Bagudá JS, Rodríguez Chaverri A, García-Cosío Carmena MD, Arribas Ynsaurriaga F, Delgado Jiménez JF. Levosimendan as bridge to transplant in patients with advanced heart failure. *Rev Esp Cardiol*. 2020;73:422–424.
9. Masarone D, Melillo E, Gravino R, et al. Inotropes in Patients with Advanced Heart Failure. *Heart Fail Clin*. 2021;17:587–598.
10. Papp Z, Agostoni P, Alvarez J, et al. Levosimendan Efficacy and Safety: 20 Years of SIMDAX in Clinical Use. *Card Fail Rev*. 2020;6:e19.
11. Silvetti S, Nieminen MS. Repeated or intermittent levosimendan treatment in advanced heart failure: An updated meta-analysis. *Int J Cardiol*. 2016;202:138–143.
12. Oliva F, Perna E, Marini M, et al. Scheduled intermittent inotropes for ambulatory advanced heart failure. The RELEVANT-HF multicentre collaboration. *Int J Cardiol*. 2018;272:255–259.
13. Yeung T, Dagan M, Lankaputhra M, et al. Levosimendan and Continuous Outpatient Support with Inotropes in Patients with Advanced Heart Failure: A Single-centre Descriptive Study. *J Cardiovasc Pharmacol*. 2022;79:583–592.
14. Gonçalves AV, Reis JP, Timóteo AT, et al. Tratamento Ambulatorial de Levosimendana por 6 Horas como Ponte para Transplante Cardíaco. *Arq Bras Cardiol*. 2023;120:e20220205.
15. de Juan Bagudá J, de Frutos F, López-Vilella R, et al. Repetitive ambulatory levosimendan as a bridge to heart transplantation. *Rev Esp Cardiol*. 2023. <http://dx.doi.org/10.1016/j.rec.2023.07.002>.