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Review Article

Levosimendan: evolution over last two decades

Kishore Gupta*, Dhiren Shah, Dhaval Naik

Department of Cardiac Surgery, CIMS Hospital, Ahmedabad, Gujarat, India

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***Correspondence:**
Kishore Gupta,
E-mail: dr_kishore24@yahoo.com

ABSTRACT

Levosimendan was maiden agent at the time of its emergence, promoting inotropy mainly through calcium sensitization of cardiac troponin C (cTnC). Levosimendan seems a lucrative option but has not demonstrated a clear superiority to other inotropes in well-designed trials. We searched the PubMed database and reviewed the pertinent studies published till 2021 and summarized various trials/studies to come to a consensus regarding its indications in cardiac patients. Patients with decompensated heart failure requiring inotropic support and receiving beta-blockers represent most widely accepted indication. Levosimendan infusions are increasingly used to facilitate extracorporeal membrane oxygenation (ECMO) weaning and avoiding hospitalizations in patients with end-stage heart failure. Levosimendan doesn't seem to have long term survival benefit in ventricular dysfunction patients undergoing surgery. The evidence supporting the role in right ventricular failure is not well-established. These lines of evidence require further investigation and their clinical significance needs to be evaluated in specifically designed prospective trials.

Keywords: Levosimendan, Heart failure, ECMO, LV dysfunction, Sepsis, Cardiorenal syndrome

INTRODUCTION

Levosimendan was maiden agent at the time of its emergence, promoting inotropy mainly through calcium sensitization of cTnC. More than two decades later it remains, remarkably, an only-in class drug, with a mechanism of action that clearly differentiates it from adrenergic agents. This augmentation of contractility is not associated with increase in calcium transients, intracellular calcium or myocardial oxygen consumption and is not compromised by pretreatment with beta blockers. It should also be noted that the interaction between levosimendan and cTnC is more intense at high, systolic ionic calcium levels than at low, diastolic calcium levels, thus avoiding impairment of myocardial relaxation upon levosimendan administration.[1]

Apart being a calcium-sensitizing agent, levosimendan also mediates the opening of ATP-dependent potassium channels (K-ATP channels) in vascular smooth muscle cells in various vascular beds. This results to increase in blood perfusion in key organs and systemic vasodilatation when levosimendan is used at doses within the recognized therapeutic range, which means that the drug must be considered and used as an indicator and not merely as an inotrope.[2]

Beyond its primary mechanisms, levosimendan has been identified as having a range of ancillary actions (pleiotropic effects) which include anti-inflammatory, antioxidative and antiapoptotic actions that may be exerted in non-cardiac organs including the kidneys, liver, gut and splanchnic vasculature, lungs and/or respiratory muscles.

Dosing

Levosimendan is given as a continuous infusion of 0.05 or 0.1 or 0.2 µg/kg/min for 24 hours, which may be preceded by a loading dose (bolus) of 6-12 µg/kg in 10 minutes. Given that the elimination half-life of dobutamine is a few

minutes while that of levosimendan is approximately 1 hour, the hemodynamic effects of dobutamine are seen almost immediately after the infusion is started, whereas a bolus of levosimendan is needed to see immediate effects. Levosimendan bolus in case of hypovolemia or initial low blood pressure could be associated with hypotension or arrhythmias.

Methods

The classical inotropic drugs are widely used in the perioperative setting, particularly in patients undergoing cardiac surgery but none of the available drugs satisfies all criteria of an ideal inotropic agent, and there is no current evidence to recommend a single molecule over the others for the daily practice. We searched the PubMed database, trials and reviewed the pertinent studies published till 2021 and summarized various trials/studies to come to a consensus regarding indications of levosimendan in cardiac sciences.

Indications for levosimendan use

Prophylactic levosimendan in cardiac surgical patients with low left ventricular ejection fraction (LVEF)

Patients with severely reduced LVEF carry a high risk of morbidity and mortality after cardiac surgery. Based on the pharmacological properties, levosimendan seemed to be an attractive option for prophylactic use in these patients for short-term benefit.

The LICORN trial aimed at assessing the efficacy of a preoperative infusion of levosimendan in reducing post-operative low cardiac output state (LCOS) in patients with poor LVEF undergoing coronary artery bypass grafting. LICORN study was a multicenter, randomized double-blind, placebo-controlled trial in parallel groups in which 340 patients with LVEF ≤40%, undergoing coronary artery bypass grafting (CABG) were recruited from 13 French hospitals and were assigned to a 24-hour infusion of levosimendan 0.1 µg/kg/min (n=167) or placebo (n=168) initiated after anesthetic induction.

Among patients with low ejection fraction who underwent CABG with cardiopulmonary bypass, levosimendan compared with placebo did not result in a significant difference in the composite end point of prolonged catecholamine infusion, use of left ventricular mechanical assist device or renal replacement therapy. These findings did not support the use of levosimendan for this indication.[3]

A meta-analysis of 16 trials (comprising of 2,273 patients) on prophylactic use of levosimendan in patients undergoing cardiac surgery showed that there was no statistically significant difference in mortality at 30 days between levosimendan and control groups. The levosimendan group had a significant reduction in acute kidney injury, intensive care unit stay and ventilation time, whereas it had higher rates of atrial fibrillation.[4]

In another study of 288 patients with preoperative LVEF ≤35%, 82 patients received 12.5 mg levosimendan starting at induction of anesthesia. Results showed thirty days mortality rates of 16% in the levosimendan group and 21% in the control group. Levosimendan showed a positive effect on post-operative renal function but a higher rate of new-onset atrial fibrillation. Three years follow up showed no differences in long-term survival between the groups.[5]

In a prospective, double-blind, randomized pilot study, effectiveness of prophylactic levosimendan in patients with impaired left ventricular function undergoing CABG was evaluated. Thirty-two patients undergoing CABG with low LVEF ≤40% were randomized to receive either a continuous infusion of levosimendan at a dose of 0.1 µg/kg/min for 24 hours without a loading dose or a placebo. Prophylactic levosimendan infusion was found safe and effective in increasing the LVEF postoperatively in patients with impaired cardiac function undergoing coronary surgery.[6]

Levosimendan had no long term or short term survival benefit when used prophylactically in cardiac surgical patients with low ejection fraction but it certainly had a role in preventing acute kidney injury in the perioperative period and reducing ventilation time as well as hospital/ICU stay.

Levosimendan in left ventricular failure

The LIDO study (levosimendan infusion versus dobutamine) compared the effects of levosimendan and dobutamine on haemodynamic performance and clinical outcome in patients with low-output heart failure. Patients were recruited into a multicenter, randomized, double-blind, double-dummy and parallel-group trial. 103 patients were assigned levosimendan and 100 dobutamine group. The primary haemodynamic endpoint was achieved in 29 levosimendan-group patients and in 15 dobutamine group. At 180 days, 27 (26%) levosimendan-group patients had died, compared with 38 (38%) in the dobutamine group. In patients with severe, low-output heart failure, levosimendan improved haemodynamic performance more effectively than dobutamine. This benefit was accompanied by lower mortality in the levosimendan group than in the dobutamine group for up to 180 days.[7]

The Levo heart shock trial was a prospective, double-blind, multicenter, randomized controlled trial comparing the early initiation of levosimendan versus placebo in patients with cardiogenic shock treated with vasopressor therapy according to a conventional strategy of inotrope use (dobutamine as first line agent). This was a double blinded trial and will be completed by 2024 and supported or refuted the role of specific inotropic agent in patients with cardiogenic shock.[8]

Levosimendan in acute decompensated heart failure

The SURVIVE study (survival of patients with acute heart failure in need of intravenous inotropic support) was a randomized, double-blind trial comparing the efficacy and safety of intravenous levosimendan or dobutamine in 1327 patients hospitalized with acute decompensated heart failure who required inotropic support. The trial was conducted at 75 centers in 9 countries and patients were randomized between March 2003 and December 2004. Despite an initial reduction in plasma B-type natriuretic peptide level in patients in the levosimendan group compared with patients in the dobutamine group, levosimendan did not significantly reduce all-cause mortality at 180 days or affect any secondary clinical outcomes.[9]

The REVIVE 2 study (evaluation of intravenous levosimendan efficacy in the short term treatment of decompensated chronic heart failure) evaluated the efficacy and safety of levosimendan, a positive inotropic drug with vasodilator effects, given intravenously to patients with acutely decompensated heart failure (ADHF). In the 600-patient trial, more levosimendan than placebo patients (58 versus 44) were improved at all 3 pre-specified time points (6 hour, 24 hour and 5 days), whereas fewer levosimendan patients (58 versus 82) experienced clinical worsening (p=0.015 for the difference between the groups). In patients with ADHF, intravenous levosimendan provided rapid and durable symptomatic relief but levosimendan was associated with an increased risk of adverse cardiovascular events.[10]

Subgroup analyses of the LIDO and SURVIVE studies, compared patients receiving beta-blockers versus those not receiving these drugs. Based on the possible beneficial hemodynamic effects, levosimendan emerged as first-choice drug in patients with acute decompensated heart failure and on beta-blockers, if beta-blockade was thought to be contributing to hypotension with subsequent hypoperfusion (class IIb, evidence level C).[11]

Levosimendan was preferred drug of choice for acute decompensated heart failure drug in comparison to classical inotropes as the latter can cause adverse effects such as tachycardia, increase ventricular rate in patients with atrial fibrillation, may induce myocardial ischemia and arrhythmias and increase mortality.

Levosimendan in patients with septic shock

Bhattacharjee et al did meta-analysis of randomized controlled trials where levosimendan was compared with dobutamine in adult patients with sepsis and septic shock and they concluded that levosimendan had no benefit in terms of mortality at longest follow up in comparison to dobutamine. However, the patients who received levosimendan had less blood lactate level and higher cardiac index.[12]

Another meta-analysis including total of 20 randomized controlled studies, where 1467 patients, with 738 patients in the experimental group (levosimendan group) and 729 patients in the control group (other inotropic drugs or placebo) was conducted found no significant differences in mortality between the levosimendan and control groups.[13]

In a multicenter, randomized, double-blind, parallel-group, placebo-controlled study a total of 2382 patients were screened at 34 centres, of whom 516 were randomized to treatment, 259 to levosimendan and 257 to placebo in the study, concluded that the addition of levosimendan to standard medical care did not reduce organ dysfunction or mortality. Levosimendan was associated with a reduced likelihood of successful extubation and an increased risk of supraventricular tachyarrhythmias.[14] Chang did a meta-analysis of randomized trials comparing the effect of levosimendan on mortality in severe sepsis and septic shock, results revealed that levosimendan could not reduce mortality in severe sepsis and septic shock.[15]

Morelli et al compared the effect of levosimendan injection and dobutamine injection on the microcirculatory blood flow in patients with septic shock. Their results showed that compared with dobutamine, levosimendan improved sublingual microcirculatory blood flow in patients with septic shock as reflected by changes in the microcirculatory flow indexes of small and medium vessels.[16]

A study conducted in 240 Chinese elderly patients concluded that there were no significant differences in mortality rates at 28 days, at ICU discharge and at hospital discharge between the two groups.[17]

Meng et al investigated the effect of levosimendan on biomarkers of myocardial injury and systemic haemodynamics in patients with septic shock. This study showed that compared with dobutamine, levosimendan reduces biomarkers of myocardial injury, improves systemic haemodynamics in patients with septic shock. However, it did not reduce the days on mechanical ventilation, length of stay in ICU and hospital or 28-day mortality.[18]

A meta-analysis of randomized trials showed that levosimendan was associated with a significant reduction in mortality compared with standard inotropic therapy.[19] However, another study by Vaitsis et al did not show that levosimendan could significantly reduce the mortality of patients with sepsis.[20]

Based on these studies and research, it seemed that levosimendan can improve cardiac function and cardiac index along with improvement in lactates but it carried no mortality benefit, hospital stay or ICU stay benefit over other inotropes or dobutamine.

Levosimendan in patients with pulmonary hypertension (PH) and right ventricular failure

A meta-analysis of ten trials including 359 participants from 6 RCTs and 4 self-controlled trials were evaluated. In the 6 RCTs, it was found that patients treated with levosimendan for 24 hours showed a significant increase in tricuspid annular plane systolic excursion and ejection fraction as well as a significant reduction in systolic pulmonary artery pressure and pulmonary vascular resistance. Adverse events did not significantly differ between the two groups and levosimendan exhibited short-term efficacy for treating right heart failure in patients with a variety of heart and lung diseases.[21]

Mishra et al compared the effects of levosimendan and milrinone in cardiac surgical patients with pulmonary hypertension and left ventricular dysfunction in which 40 patients were allocated randomly to receive either milrinone, 50 µg/kg bolus followed by infusion at a rate of 0.5 µg/kg/min (group 1) or levosimendan 10 µg/kg bolus followed by infusion at a rate of 0.1 µg/kg/min (group 2) for 24 hours after surgery. The study demonstrated that levosimendan was not clinically better than milrinone. Levosimendan therapy resulted in a greater increase in heart rate, decrease in systemic vascular resistance, and a greater need for norepinephrine than in patients who received milrinone.[22]

Despite using vasoactive and PH specific therapies, the in-hospital mortality of severe PH with right heart failure (RHF) remained high. Intravenous levosimendan effectively improved severe RHF of PH patients in hospital and well tolerated in a group of 45 hospitalised patients of pulmonary hypertension, levosimendan was administered at the rate of .05-0.1 µg/kg/min, up to a total dose of 12.5 mg. 7th day after levosimendan infusion, seven out of 13 PH patients with WHO-FC IV improved by one class (p=0.008). Borg dyspnea scores, 6-min walk distance and NT-pro BNP improved significantly (p<0.001). Compared with baseline, the right atrial transverse dimension, end-systolic eccentricity index and tricuspid annular plane systolic excursion improved significantly (58.8±13.1 mm versus 53.7±12.4 mm; 1.50±0.27 versus 1.38±0.23; 15.0 (13.0, 16.0) mm versus 15.8 (14.0, 17.4) mm, p<0.005, respectively).[23]

HELP trial (a randomized placebo-controlled trial) was conducted with the purpose of evaluating the effects of intravenous levosimendan on hemodynamics and 6-min walk distance (6MWD) in patients with pulmonary hypertension and heart failure with preserved ejection fraction (PH-HFpEF). Compared with placebo, levosimendan did not significantly reduce the primary end point of exercise-PCWP at 6 weeks. However, levosimendan reduced PCWP measured across all exercise stages. Six weeks of once-weekly levosimendan infusion did not affect exercise-PCWP but did reduce PCWP incorporating data from rest and exercise, in tandem with increased 6MWD.[24]

The existing literature did not provide adequate evidence to currently recommend the use of levosimendan as definite therapy in PH and associated RV failure.

Levosimendan to facilitate weaning from veno-arterial ECMO oxygenation

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provided a temporary support system for patients with cardiogenic shock refractory to conventional medical therapies. ECMO weaning can, however, be challenging and lead to circulatory failure and death. Various studies suggested a potential benefit of levosimendan for ECMO weaning.

A retrospective COHORT study was conducted in a French university hospital from 2010 to 2017. A total of 150 patients in ICU undergoing VA-ECMO were studied and it was found that levosimendan was the only factor associated with a significant reduction in VA-ECMO weaning failure rates. After propensity score matching analysis, the difference in 30-day mortality between the two groups was found not significant.[25]

In a systematic review and meta-analysis investigating whether levosimendan offered advantages compared to standard therapy or placebo, in cardiogenic shock adult patients treated with VA-ECMO. There was a significant increase in successful weaning with levosimendan compared to the controls. A decrease risk of all-cause mortality in the levosimendan group was also observed.[26]

In a retrospective study, before-and-after study group comparisons between patients treated with levosimendan and patients treated with milrinone were made. Levosimendan enabled ECMO weaning without increasing norepinephrine requirements when compared to a control group receiving milrinone.[27]

An observational single-center COHORT study where all patients undergoing VA-ECMO over 6 years were divided into levosimendan group and control group. The primary endpoint was VA-ECMO weaning failure defined as death during VA-ECMO treatment or within 24 hour after VA-ECMO removal. Secondary outcomes were mortality at day 28 and at 6 months. The rate of weaning failure was 29.1% and 35.4% in levosimendan and control groups, respectively (OR: 0.69, 95% CI: 0.25-1.88). No significant difference was observed between groups for all secondary outcomes. Levosimendan did not improve the rate of successful VA-ECMO weaning in patients with refractory cardiogenic shock.[28]

Seven studies of observational design, comprising a total of 630 patients were selected for observing the success of weaning from VA-ECMO. The VA-ECMO durations varied between four and 11.6 days. Overall, levosimendan use was significantly associated with successful weaning compared with control (odds ratio [OR] 2.89, 95% CI, 1.53-5.46; p=0.001); I^2=49%). Levosimendan therapy was

significantly associated with successful weaning and survival benefit in patients with cardiogenic or postcardiotomy shock needing VA-ECMO support for severe cardiocirculatory compromise.[29]

Levosimendan use in VA-ECMO patients seemed to reduce weaning failure regardless of the initial etiology and to reduce mortality when administrated early after VA-ECMO initiation. WEANILEVO trial (a randomized, prospective, multicenter, double-blind, parallel-group, controlled trial) will be evaluating whether administration of levosimendan before VA-ECMO weaning was associated with a reduced rates of weaning failure and recourse to other temporary circulatory support. 180 patients were enrolled if they had acute circulatory heart failure treated with VA-ECMO and for whom weaning was expected within 48 hour. The study drugs were either levosimendan (0.2 µg/kg/min for 24 hour) or a placebo. The primary endpoint of the trial was the absence of VA-ECMO weaning, recourse to another VA-ECMO or other temporary circulatory assistance or death within 7 days of VA-ECMO weaning. The results of WEANILEVO should significantly influence decisions regarding the use of levosimendan for VA-ECMO weaning.[30]

Levosimendan might potentially remain useful in successful weaning of VA ECMO in ICU patients and reducing weaning failure rates but the results of WEANILEVO trial were much needed to support the other retrospective studies. Levosimendan had no added benefit for ECMO weaning in patients with refractory cardiogenic shock.

Repetitive infusions of levosimendan in patients with advanced chronic heart failure

The LEVOREP study (efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure) determined whether intermittent ambulatory treatment with levosimendan would improve functional capacity, quality of life and event-free survival in patients with advanced heart failure. This was a prospective, randomized, double-blind, placebo-controlled, multicenter, parallel-group trial of pulsed infusions of levosimendan in 120 outpatients with advanced heart failure (EF ≤35%, NYHA class III or IV). The study was conducted at 11 centres in Austria, Greece and Germany. Levosimendan (0.2 µg/kg/min) or placebo was administered for 6 hours at 2-week intervals over 6 weeks, in addition to standard care therapy. The primary outcome was the proportion of patients with a ≥20% improvement in the 6 min walk test and a ≥15% score increase on the Kansas City cardiomyopathy questionnaire at the end of the 24-week study period. Secondary outcomes included event-free survival after 24 weeks. Analyses were performed on an intention-to-treat basis. The primary endpoint was reached in 19% of patients receiving levosimendan and 15.8% of patients receiving placebo (odds ratio 1.25; 95% CI 0.44-3.59; p=0.810). Cardiac death (four versus one), heart transplants (two versus one) and acute heart failure (14 versus nine) were more frequent with placebo as compared with levosimendan. The incidence of side effects was comparable between groups. Intermittent ambulatory treatment with levosimendan in patients with advanced heart failure did not improve significantly functional capacity or quality of life as compared with placebo.[31]

Table 1: Findings from recent studies.

Indication/role	Conditions	Benefits
Definite	Acute decompensated heart failure	Preffered drug of choice for those on beta-blockers
	VA-ECMO weaning	Better survival, lower weaning failure rates, WEANILEAVO trail awaited
	Cardio-renal syndrome	Better survival
Probable	Left ventricular failure	Improves hemodynamic performance, lowers mortality but results from LEVOHEART trial awaited
	Advanced chronic heart failure	Bridging therapy and ameliorating symptoms.
Marginal	Cardiac surgery in Low EF group	No survival benefit but lowers AKI and ICU/Hospital stay
	Pulmonary hypertension in RV failure	Short term efficacy but no exercise benefit
No role	Sepsis	Higher mortality rates

The LION-HEART study was a multicenter, double-blind, randomized, parallel-group, placebo-controlled trial evaluated the efficacy and safety of intravenous administration of intermittent doses of levosimendan in outpatients with advanced chronic heart failure. Sixty-nine patients from 12 centers were randomly assigned at a 2:1 ratio to levosimendan or placebo groups, receiving treatment by a 6-hour intravenous infusion (0.2 µg/kg/min without bolus) every 2 weeks for 12 weeks. In this small pilot study, intermittent administration of levosimendan to ambulatory patients with advanced systolic heart failure reduced plasma concentrations of NT-proBNP, worsening of HRQoL and hospitalization for heart failure. In comparison with the placebo group, the patients on levosimendan experienced a reduction in the rate of heart failure hospitalization (hazard ratio 0.25; 95% CI: 0.11-0.56; p=0.001) and were less likely to experience a

clinically significant decline in HRQoL over time (p=0.022).[32]

The incidence of serious adverse events in patients with advanced chronic heart failure waiting for a heart transplantation or a long-term mechanical assist device were not different between treatment and placebo groups, reflected the safety of repetitive infusions of levosimendan as a stabilization therapy. However, it was important to mention that although mortality and readmission rates decreased with levosimendan but it cannot be considered as an alternative to definite therapy. It alleviated the symptoms and improved the quality of life in patients awaiting transplantation or in those who were ineligible for more invasive approaches. Results from a new RCT LeoDOR trial were awaited to confirm the usefulness of repeated infusions of levosimendan in this patient population.

Levosimendan and cardiorenal syndrome

The emphasis on preservation of renal function in clinical management protocols reflected appreciation of the relation between worsening kidney function and deterioration of prognosis in AHF.

Renal dysfunction was very common in HF and a further worsening of kidney function may be expected during hospitalization for AHF. The treatment of cardiorenal syndrome in decompensated HF was challenging due to variable pathophysiology and lack of specifically tailored therapeutic options. Identifying the underlying processes of kidney dysfunction was essential to successful management. Volume status should be checked whenever possible as well as hypotension and third space fluid accumulation. Inotropes may be appropriate for short-term management of AHF with renal dysfunction; especially, in low-output states, they may be particularly indicated to avoid renal hypoperfusion.

Levosimendan, both in the acute setting and in the repetitive/intermittent context of AdHF, appeared to a promising option to improve renal perfusion or to reverse or ameliorate renal dysfunction but further controlled trials were needed to confirm the status of levosimendan for this purpose. A continuous 24-hour infusion of levosimendan should be administered at a rate of 0.05-0.1 µg/kg/min, while maintaining the patient in euvolemic and eukalemic state. Levosimendan, in acute decompensated HF, had an immediate reno-protective effect, mediated by an increase in renal blood flow, due to a selective renal arterial and venous vasodilating action.[33-35]

CONCLUSION

The present review summarized the available evidences from trials, meta-analysis and consensus documents on levosimendan use in the context of cardiac sciences, highlighting the findings from more recent studies (Table 1).

Patients with decompensated heart failure requiring inotropic support and receiving beta-blockers represent the most widely accepted indication. ECMO weaning, bridge to stabilization in end-stage heart failure, cardiorenal syndrome seems other favourable indications. Long term survival benefit in low ejection fraction cardiac surgical patients is still not evidence supported as in pulmonary hypertension and right ventricular failure. These lines of evidence require further investigation and their clinical significance needs to be evaluated in specifically designed prospective trials.

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