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CARDIOVASCULAR ANESTHESIA (J FASSL, SECTION EDITOR)

Levosimendan: What Have We Learned So Far?

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Abstract

Purpose of Review Vasoactive therapy represents a pivotal yet debated topic in critically ill patients and in those with chronic heart failure. Levosimendan, a calcium sensitizer agent with inodilating properties, has been in the market for 27 years and new indications came out over time. The aim of the present review is to highlight what is actually proven and what is debated on the use of levosimendan in light of its pharmacologic features and the pathophysiological evidence.

Recent Findings Levosimendan was firstly seen as an inodilator acting through calcium sensitization in myocytes both in the myocardium and in vascular smooth muscle. Over the years, its anti-inflammatory properties became clearer and a role in preconditioning and weaning from mechanical circulatory support was postulated. More recently, a possible action on other muscular fibers, namely, diaphragmatic myocytes, was observed, leading to a possible application in mechanical ventilation-related diaphragmatic dysfunction.

Summary Preliminary data showed promising effects of levosimendan in patients with sepsis-related and stress-related (Takotsubo) myocardial dysfunction, in those difficult-to-wean from mechanical circulatory support and in ventilator-associated diaphragmatic dysfunction. Moreover, its vasodilating, anti-oxidant, and neuroendocrine properties pave the way to a number of additional possible applications. Larger studies yielding to more conclusive results on these indications are under way or need to be planned in the future.

Keywords Levosimendan · Vasoactive therapy · Shock · Weaning · Inotrope

Introduction

From its very first report in the medical literature [1], through the last 27 years, levosimendan has been widely used in clinical practice and tested in clinical trials in patients with acute or chronic cardiac failure or to stabilize at-risk patients undergoing cardiac surgery.

Due to its effect beyond inotropism, levosimendan has also been used in other situations and conditions.

The present review will focus on the evidence gained so far, considering the pathophysiological plausibility in the different settings.

Levosimendan, Major Mechanism of Action

Levosimendan exhibits multiple effects. It has been primarily used for its inotropic action: it is exerted by binding to troponin C and increasing myocyte sensitivity to calcium, without increasing myocardial oxygen consumption.

Biochemical properties of levosimendan also involve an active long-lived metabolite, OR-1896 (the (−) enantiomer of N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl) phenyl] acetamide). Indeed, unlike levosimendan, with its short elimination half-life, the half-life of OR-1896 is longer (1–1.5 h vs 75–80 h), explaining the persistence of clinical

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cardiovascular effect for 7–9 days after the end of 24-h infusion. Due to the renal and liver elimination, patients with severe kidney and moderate liver dysfunction may benefit from levosimendan effects longer.

Throughout the years, it has been demonstrated that levosimendan has interactions with more than one molecular target within the cardiovascular system (Table 1).

Levosimendan in Acute and Chronic Heart Failure

Levosimendan presents with peculiar properties that make it promising in heart failure patients. In fact, the ability to improve both systolic and diastolic functions without increasing myocardial oxygen consumption led to its use in patients with decompensated heart failure, and its safety in post-myocardial infarction heart failure has been established. The positive effects of levosimendan on inotropism have been confirmed both in healthy volunteers and in patients with decompensated heart failure at 6–24 μg/kg bolus doses followed by 0.1–0.4 μg/kg/min for 1–24 h. [2–7] The initial bolus was intended to speed up the clinical effect but accounted for the majority of serious hypotensive events leading to discontinuation of levosimendan and has hence been abandoned in clinical practice over the years.

In early clinical studies in patients with heart failure, levosimendan had favorable effects on cardiac symptoms, hospitalization, and risk of death [8–12].

In the placebo-controlled RUSSLAN study, levosimendan decreased the incidence of worsening heart failure and reduced both short-term and long-term mortalities. Sonntag et al. demonstrated that levosimendan infusion induced reductions in the number of hypokinetic segments in the left ventricle and increased LVEF, suggesting a counteracting role in post-ischemic stunning. In addition, pulmonary arterial pressure decreased in the levosimendan group but not in the placebo group. [13] Intravenous levosimendan has more beneficial hemodynamic actions than placebo (6-h infusion) or intravenous dobutamine (24-h infusion) in patients with decompensated heart failure, including those with acute myocardial infarction. A consistent beneficial effect of levosimendan on symptoms of dyspnea and fatigue has not been demonstrated, although some favorable data have been reported [9, 10].

The randomized, double-blind SURVIVE trial remains the largest head to head comparison of efficacy and safety of intravenous levosimendan or dobutamine of in the AHF following AMI. [14] No evidence in favor of levosimendan vs dobutamine was found in the study. A natural question arises why some clinical trials of levosimendan produced statistically significant evidence of survival benefit while others did not reach significance or were neutral [14, 15].

As already highlighted by an expert review, [16] discrepancies in the results might be due to the baseline differences of enrolled populations (e.g., possible hypotension, arrhythmias, and concurrent pharmacological treatments). Moreover, additional and still unclear factors may account for differences in response to the drug. As for all vasoactive drugs, correction of hypovolemia when present is paramount before starting inotropic support [16].

In a recent meta-analysis, levosimendan proved effective in reducing mortality in patients with heart failure when compared to dobutamine at the final follow-up to 12 months, while no statistically significant difference was observed in short (< 30 days) and midterm (30 days–6 months) mortalities [17]. Levosimendan treatment was associated with improvements in hemodynamic and cardiac parameters and carried significant differences in extrasystoles, hypotension, and headache or migraine were observed.

In the particular setting of cardiogenic shock complicating AMI, survival at 30 days was significantly in favor of levosimendan vs enoximone [18] and tended to require less additive catecholamines treatment.

Accordingly, in the study by Christoph et al. [19], the infusion of levosimendan resulted in early and sustained hemodynamic improvement as compared to intra-aortic balloon pump placement in patients with acute myocardial infarction (AMI) and refractory cardiogenic shock (CS) following preliminary hemodynamic support (dobutamine with or without norepinephrine) and primary percutaneous coronary

Table 1 Major mechanisms of levosimendan

Positive inotropism	Calcium sensitization by saturating troponin C myofilaments of the cardiomyocytes.
Vasodilation	Hyperpolarization by ATP-sensitive K^+ channels existent on the sarcolemma of vascular smooth muscle cells
Cardioprotection	Protection of mitochondria in ischemia-reperfusion mechanism in the cardiomyocytes
Phosphodiesterase inhibition	cAMP elevation caused by alterations in intracellular Ca2+ concentration
Neurohormone, cytokine, and biomarker properties	Not entirely understood, several cellular processes involved (from preservation of endothelial function to the inhibition of platelet aggregation)

intervention (PCI). Furthermore, cardiac index rose more rapidly in the levosimendan arm, and systemic vascular resistance showed a more pronounced initial decrease.

Recently, in the setting of advance heart failure (AdHF), intermittent cycles of intravenous levosimendan showed encouraging findings which have emerged from a range of exploratory studies and from three larger controlled trials (LevoRep, LION-HEART, and LAICA) [20, 21, 22•] suggesting that levosimendan can be a valid option to avoid a further loss of LV function and burden the rehospitalization [23].

Levosimendan in Cardiac Surgery Patients

Patients undergoing aortic valve replacement (AVR) surgery combined with coronary artery bypass grafting (CABG) are at risk for left ventricular (LV) dysfunction [24] and adequate oxygen delivery and normal mixed venous saturation (S_{VO_2}) values during the immediate postoperative period after cardiac surgery can decrease morbidity and, therefore, reduce the length of the hospital stay [25].

In a small 24-patient randomized trial [26], levosimendan infusion 24 h before cardiac surgery was compared to placebo in patients with LVEF < 50% or LV hypertrophy: a significant difference was found in terms of CI and stroke volume index for the 4-day postoperative period.

A Bayesian meta-analysis conducted by Greco et al. showed that levosimendan seems to be the most effective drug in decreasing mortality after cardiac surgery [27].

Conversely, at the beginning of 2017, two randomized controlled trials (RCTs) were not able to show beneficial effects on mortality from the use of levosimendan compared with placebo in patients with preoperative severely depressed LVEF or in a mixed population of patients with either preoperative severely depressed LVEF or both intra- and postoperative cardiovascular dysfunction [28•, 29•]. Both these RCTs had relevant limitations. In particular, the Landoni study [28•] investigated a non-selected population (i.e., the cause for hemodynamic impairment was not specified), used low-dose levosimendan, and the hemodynamic effect of the drug (namely on cardiac output) was not routinely measured; hence, the assumptions that patients needed an inodilator and that a lower-than-normal dosage of levosimendan carried out the same cardiovascular effects are seem not substantiated by evidence. The Mehta study [29•], on the other hand, demonstrated that low ejection fraction per se does not justify the prophylactic use of levosimendan in patients undergoing cardiac surgery; however, the administration of the drug led to a reduction in the episodes of low-cardiac output and in the need for other inotropes beyond 24 h from the beginning of the infusion. Overall, the main conclusion we can draw based on these RCTs is that indiscriminate use of levosimendan in unselected populations, either in a prophylactic fashion or for treatment of hemodynamic instability, is not justified.

In a recent meta-analysis [30••], the overall mortality was similar in the levosimendan and the placebo population, but levosimendan infusion showed a significantly lower mortality in the low LVEF (< 35%) subgroup. Moreover, a non-significant trend has been shown toward a lower incidence of support with levosimendan, both overall and in the subgroup with low LVEF.

As secondary endpoint, on the basis of pooling the results of three studies, levosimendan significantly reduced the risk of AKI compared with placebo [28•, 31, 32].

Furthermore, a reduced myocardial damage as assessed by postoperative cTnI concentrations has been shown in patients undergoing cardiac surgery and pretreated with levosimendan [33], consistent with the results of the meta-analysis conducted by Zangrillo et al. [34] It was hypothesized that these results could be explained by anti-aggregatory clinically effect of levosimendan, but the present knowledge regarding this potentially very important side effect of levosimendan is insufficient.

A meta-analysis conduct by Chen et al. showed that levosimendan therapy was associated with reduced mortality in patients with preoperative LV dysfunction (< 40%), in less renal replacement therapy and shorter ICU stays. However, patients with normal LV systolic function did not benefit from levosimendan therapy. Authors highlighted how levosimendan should be used with caution in patients with hemodynamic instability, due to a significantly increased incidence of hypotension [35].

Although a moderate bulk of evidence has accumulated in the last 5 years about the role of levosimendan in mortality among cardiac surgery patients, 2 large RCTs (CHEETAH and LEVO-CTS) failed to show any survival benefit with levosimendan administration in cardiac surgery patients [28•, 29•, 36, 37, 38••]. However, the recent update consensus process [39••] recommend the use of levosimendan in low ejection fraction patients undergoing CABG to reduce mortality (GRADE 1B) with a concordance of 55% among the experts.

Levosimendan in Pulmonary Hypertension

According to its pharmacodynamic profile, levosimendan could be a potential agent for the treatment of right ventricular failure caused by pulmonary hypertension (PH) and right heart failure.

The effect of levosimendan on PH and associated RV failure has been assessed using a wide range of different animal models of acute and chronic PH, and several of these

preclinical studies have shown beneficial effects of levosimendan [40–43].

Results similar to what has been shown in preclinical studies have been reported in patients with PAH; however, data are very sparse and not conclusive [44–47, 48•].

Also in the subgroup of PH due to left heart failure, the results among the studies did not show univocal significant evidence in the use of levosimendan [49–52].

Only very few levosimendan studies have been conducted in PH associated with lung disease and in PH related to pulmonary thromboembolism, and results are not comparable [53–55].

A possible explanation of these ambiguous results is that in the context of PH, most clinicians avoid administering a loading dose of levosimendan due to its side effects while increasing the infusion dose when needed. This prevents the plasma concentration of the drug to reach PDE-inhibiting levels.

The current evidence is hence not conclusive for the use of levosimendan in PH.

Levosimendan in the ICU

Levosimendan seems to be the ideal drug for the ICU patient: hemodynamic support, increased ejection fraction and cardiac index without increasing of oxygen consumption, peripheral vasodilation and reduction of tissue and organ hypoperfusion, increased GFR and renal function, and decreased need for catecholamines.

Levosimendan has been studied in the context of sepsis-related cardiomyopathy (SRC). SRC has a prevalence up 60% of patients with septic shock and may play a role in the patient's outcome [56–58].

In a mono-centric randomized controlled study in septic patients, 24-h infusion of levosimendan was associated with an increase in cardiac output and a reduction in pulmonary congestion, with no increase in vasopressor requirements (owing to volume expansion) and with more favorable evolution of various MOF surrogates (lactate clearance, venoarterial carbon dioxide gap, gut mucosal perfusion, and renal function); contrariwise dobutamine did not alter any of these variables [56]. Following this trial, many other studies have been conducted about the use of levosimendan in septic shock [56–59, 60•, 61], and their results have been incorporated into a meta-analysis of the effects of levosimendan in septic shock vs standard inotropes that showed a significant reduction in mortality in the levosimendan group, without intergroup differences in MAP or norepinephrine usage yet [62]. Nevertheless, a multicenter randomized placebo-controlled trial of levosimendan in sepsis (LeoPARDS) did not fulfill the primary end point of a significant intergroup difference in mean daily Sequential Organ Failure Assessment (SOFA) score favoring levosimendan nor was mortality reduced [63].

As suggested by Herpain et al. [64••], currently available clinical evidence is that levosimendan can successfully replace dobutamine in supporting severe de novo acute heart failure (AHF) due to septic cardiomyopathy (SCM). Indiscriminate use of levosimendan (i.e., without selecting severe cases of cardiovascular failure) to prevent the development of MOF is safe but does not confer a clinical benefit.

Furthermore, in the particular subgroup of patients with cardiorenal syndrome, levosimendan should be preferred vs dobutamine as an inotropic drug. In fact, the study by Lannemyr et al. showed that both levosimendan and dobutamine increase renal blood flow with no significant difference between the two-groups (levosimendan vs dobutamine), but glomerular filtration increased significantly in patients receiving levosimendan ($p = 0.012$), while dobutamine decreased the filtration fraction by 17% [61].

Levosimendan in the Difficult-to-Wean Patient

Levosimendan has also been used in difficult-to-wean patients, with the hypothesis that it could have a role in enhancing muscular contractility not only in the cardiac muscle but also in the respiratory muscles (in particular the diaphragm). Positive effects were seen in both slow and rapid diaphragm muscle fibers [65–67], and some studies in this field are now ongoing. It has also been demonstrated that levosimendan, compared with dobutamine, could be a useful treatment in difficult-to-wean patients with chronic obstructive pulmonary disease [68]. Most patients require inotropic drugs to support myocardial contractile function during weaning from VA-ECMO; the infusion of levosimendan 24 h before the weaning trial from VA-ECMO was associated with a significant reduction (about 50%) in the need for inotropic and/or vasopressor support [69] and the weaning success rate was significantly higher even if the difference in survival rate was substantial but not statistically significant. On the contrary, in the retrospective analysis conducted by Distelmaier et al. [70•] on patients on VA-ECMO after cardiovascular surgery, patients in the levosimendan group had a significantly lower 30-day mortality and better long-term survival. Furthermore, endothelial function after levosimendan infusion in patients on VA-ECMO has been demonstrated to improve, adding this beneficial effect of levosimendan to the improvement in cardiac function in weaning from ECMO [71•]. Following this beneficial influence on endothelin receptors, an experimental study on the role of levosimendan in preventing delayed cerebral vasospasm in an in vitro rabbit model induced subarachnoid hemorrhage in an in vitro rabbit model. The use of levosimendan seems to restore the impaired function of the endothelin receptor and also reverse the PFG-induced

contraction, suggesting a possible role in antagonizing the cerebral vasospasm in SAH patients [72].

Levosimendan in Pediatric Patients

Even if the use of levosimendan in the pediatric population is off-label, studies have been conducted on its use not only in patients undergoing cardiac surgery but also in settings of chronic heart failure, sepsis, and cancer-associated cardiac dysfunction [73–81].

A meta-analysis of randomized controlled trials comparing levosimendan vs any comparator (milrinone, dobutamine, and standard inotropic treatment) suggested a beneficial effect on hemodynamic parameters, but no difference was found in ICU length of stay (LOS) and mortality [82].

Levosimendan in the Takotsubo Syndrome

Takotsubo (TT) is a complex and multifactorial syndrome mimicking a myocardial infarction, of which the underlying etiopathology has not been completely elucidated [83]. One of the causes proposed is a massive sympathetic activation mediated also by a catecholamine surge acting at cardiomyocytes and causing the typical contractility impairment. Recent registries have demonstrated that up to 10% of patients affected by TT present with cardiogenic shock [84]. Since catecholamine serum levels are elevated in patients with TT exogenous inotropes, acting on α and β receptors should be possibly avoided [85] or at least at the lowest possible dose and for the shortest time since it could also sustain the syndrome's causative factors in patients without left ventricular outflow tract obstruction [86••]. An elegant study performed on animal models has demonstrated the negative inotropic effect enhanced by epinephrine and that levosimendan was effective in reversing the negative inotropic effect of epinephrine without increasing mortality. This has been also reported in a number of case series in the literature [87].

Conclusion

Data in literature suggest a possible alternative use for levosimendan in therapeutic areas in which preconditioning may be beneficial, such as in the settings of cardiac surgery, both in pre- or postoperative period and in the reduction of ischemic adverse events after CABG surgery. Levosimendan also improves long-term survival in acute and chronic heart failure, and particularly in the subgroup of patients with chronic heart failure and renal impairment, levosimendan should be the first choice of inotropic agents.

The longer action of its active metabolite is probably the main actor of its hemodynamic effects. However, it is still uncertain if the long-lived metabolites of levosimendan have similar cardioprotective effects as the parent molecule: further preclinical and clinical data are required to verify it.

In the next future, levosimendan could also play a role in other clinical conditions due to its vasodilatory, neuroendocrine, and anti-oxidant effect.

To date, the two largest RCTs on the use of levosimendan in cardiac surgical patients [28•, 29•] do not justify an indiscriminate use of the drug, and even if improvement on survival rate may be plausible, further in-depth assessment of the utility of levosimendan will require additional trials, in well-defined subgroup patient populations in order to reduce possible bias and non-conclusive results.

Compliance with Ethical Standards

Conflict of Interest Giulia Villa, Guido Tavazzi, Fabio Guarracino, and Fabio Sangalli declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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