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REVIEW

Peri-operative Levosimendan in Patients Undergoing Cardiac Surgery: An Overview of the Evidence

William Y. Shi, MBBS [a,b,c*], Sheila Li, BMed [a], Nicholas Collins, FRACP [b], David B. Cottee, PhD, FANZCA [d], Bruce C. Bastian, FRACP [b], Allen N. James, FRACS [a], Ross Mejia, FRACS [a]

[a]Department of Cardiothoracic Surgery, John Hunter Hospital, Newcastle, NSW, Australia
[b]Department of Cardiovascular Medicine, John Hunter Hospital, Newcastle, NSW, Australia
[c]The University of Melbourne, Australia
[d]Department of Anaesthesia, John Hunter Hospital, Newcastle, NSW, Australia

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Levosimendan, a calcium sensitiser, has recently emerged as a valuable agent in the peri-operative management of cardiac surgery patients. Levosimendan is a calcium-sensitising ionodilator. By binding to cardiac troponin C and reducing its calcium-binding co-efficient, it enhances myofilament responsiveness to calcium and thus enhances myocardial contractility without increasing oxygen demand. Current evidence suggests that levosimendan enhances cardiac function after cardiopulmonary bypass in patients with both normal and reduced left ventricular function. In addition to being used as post-operative rescue therapy for low cardiac output syndrome, a pre-operative levosimendan infusion in high risk patients with poor cardiac function may reduce inotropic requirements, the need for mechanical support, the duration of intensive care admissions as well as post-operative mortality. Indeed, it is these higher-risk patients who may experience a greater degree of benefit. Larger, multicentre randomised trials in cardiac surgery will help to elucidate the full potential of this agent.

Keywords Levosimendan • Cardiac surgery • Heart failure • Ventricular function • Myocardial function

Introduction

Despite improvements in percutaneous and transcatheter therapies for cardiovascular disease, cardiac surgery remains the standard of care in many clinical situations. In particular, patients with complex coronary anatomy [1], diabetes mellitus [2] and valvular heart disease are frequently best served by proceeding to surgery. As the population ages, patients referred for surgery are increasingly more frail and of higher peri-operative risk given their co-morbidities and physiological derangements [3,4].

This is particularly the case in patients referred for surgery who have severe left ventricular dysfunction. Indeed, peri-operative myocardial dysfunction is associated with organ failure, prolonged intensive-care stay, delayed recovery and prolonged hospital admissions [5,6]. These patients also often require a longer period of inotropic support, using agents such as catecholamines which themselves carry deleterious side-effects such as tachycardia, an increase in systemic afterload and myocardial oxygen demand [7]. In addition, phosphodiesterase inhibitors such as milrinone, while commonly used, may have negative effects on neurohormone levels and intracellular calcium [8,9].

Levosimendan, a calcium sensitiser, has more recently emerged as an alternative agent in such scenarios. While currently utilised mainly for decompensated heart failure, it

*Corresponding author at: Corresponding author. Department of Cardiothoracic Surgery, John Hunter Hospital, Lookout Road, New Lambton NSW 2305, Australia. Tel.: +61 2 4921 3534; fax: +61 2 4921 4544., Email: william.y.shi@gmail.com

may play an important role as a peri-operative agent in cardiac surgery. The article will provide an overview of the properties of levosimendan and the major studies evaluating the impact of levosimendan in patients undergoing cardiac surgery.

Levosimendan

Mechanism of Action

Traditional inotropic agents such as adrenaline and dobutamine stimulate beta-1 adrenergic receptors causing an increase in concentrations of cyclic adenosine monophosphate (cAMP), while phosphodiesterase inhibitors inhibit the breakdown of cAMP by phosphodiesterase. Increases in cAMP levels result in an up-regulation in the levels of protein kinase C, which increases the calcium current into myocytes during systole to create a positive inotropic effect [10].

On the other hand, levosimendan is a calcium-sensitising inodilator. By binding to cardiac troponin C and reducing its calcium-binding co-efficient, it enhances myofilament responsiveness to calcium and thus enhances myocardial contractility without increasing oxygen demand. Furthermore, levosimendan activates adenosine triphosphate-sensitive potassium channels (K_{ATP}). This produces vasodilatation of the coronary vasculature and mitochondrial activation, which serve to further improve myocardial performance [10–15]; of note, levosimendan also contributes to vasodilatation in other vascular beds, producing a tendency for hypotension [16]

Pharmacokinetics

Levosimendan is administered via a continuous intravenous infusion following a weight based loading dose. Levosimendan exhibits a linear pharmacokinetic profile, and a half-life of one hour [17–19]. It is distributed rapidly to tissues with up to 98% being bound to mainly plasma albumin [19]. In the gastrointestinal tract, it is reduced to an amine metabolite (OR-1855) which is acetylated to an active metabolite (OR-1896). The half-life of OR-1896 is approximately 80 hours, while still exhibiting a similar haemodynamic profile to levosimendan. This likely explains the long-lasting haemodynamic effects after an infusion of levosimendan [20,21], with sustained improvements in natriuretic peptide levels and ventricular performance when compared to alternate inotropic agents. The pharmacokinetics are relatively unaltered by age, gender and organ dysfunction [22]. Of note, levosimendan does not interact appreciably with commonly used cardiovascular drugs such as beta blockers, digoxin, warfarin, isosorbide mononitrate and carvedilol [11]. The hypotension noted followed by peripheral vessel vasodilatation may be ameliorated by omission of the loading dose [16].

Levosimendan in Heart Failure

Levosimendan has been shown to be efficacious in the management of heart failure, though there is conflicting data in this area. Multiple randomised trials have shown levosimendan to be associated with improved haemodynamics, improvements in cardiac function, shorter stay in a high dependency unit as well as reduced mortality compared to placebo or dobutamine [23–26]. One of the largest studies, the randomised study on safety and effectiveness of levosimendan in patients with left ventricular failure due to an acute myocardial infarct (RUSSLAN) trial, enrolled 504 patients and randomised them to either levosimendan or placebo. In this double-blind study, those in the levosimendan group experienced reduced mortality compared to placebo at 14 days (11.7% vs. 19.6%, p=0.031) as well as 180 days (22.6% vs. 31.4%, p=0.053). The REVIVE II trial randomised 600 patients with acute decompensated heart failure to either levosimendan plus standard therapy or a placebo infusion plus standard therapy. The primary endpoint was a composite clinical endpoint of clinical improvement or deterioration as per a global assessment at various time points. At five days, more patients receiving levosimendan experienced improvement compared to those in the placebo group (19.4% vs. 14.6%, p=0.015) while fewer in the levosimendan group worsened compared to placebo patients (19.4% vs. 27.2%). Though not powered to investigate mortality, there were no differences between groups with respect to mortality at 90 days [27,28].

By contrast, the SURVIVE trial, which randomised 1327 patients hospitalised with acute decompensated heart failure to either levosimendan (n=664) or dobutamine (n=663) in a blinded fashion, found that despite an initial reduction in plasma B-type natriuretic peptide level amongst the levosimendan patients, there were no differences between the study arms in all-cause mortality at 180 days or any other secondary endpoints [26].

Levosimendan in Cardiac Surgery

Over past decades, centres around the world have noted an increasing risk profile in those referred for cardiac surgery [3,4]. Furthermore, there is evidence suggesting that patients with both coronary artery disease and reduced left ventricular function benefit from coronary surgery over medical therapy [29]. Patients with left ventricular dysfunction represent a substantial peri-operative challenge, as they experience higher rates of mortality and other adverse outcomes [5,6,30]. It is in such patients that levosimendan is a particularly attractive option.

Several randomised trials have been reported comparing levosimendan to either dobutamine, milrinone, placebo, or an intra-aortic balloon pump (IABP) [16,31–43]. In these studies, levosimendan was administered either pre-, intra- or post-operatively, to patients with either preserved, or impaired LV function.

Three meta-analyses have suggested a mortality benefit in cardiac surgery patients receiving levosimendan. Landoni and colleagues [44] found that levosimendan reduced mortality with an OR of 0.35 (95% CI 0.18 – 0.71, p = 0.003) while Maharaj et al. [45], in a meta-analysis of levosimendan in percutaneous and surgical revascularisation, found a mortality benefit with an OR of 0.40 (05% CI 0.21 – 0.76, p = 0.005). The most recent