

Case Report

Levosimendan in the Perioperative Period of Cardiac Surgery: a Case Report and Mini Review

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Abstract

The authors describe a case of a patient with severe ischemic heart disease who benefited from the combination of Levosimendan with intra-aortic balloon pump in the perioperative period of a triple coronary artery bypass graft. On this occasion, they review the literature on the benefits of levosimendan in this indication in terms of hemodynamics, renal function and mortality.

Introduction

Levosimendan is a calcium-sensitizing inotrope drug and also an ATP-sensitive potassium (KATP) channel opener that results in significant vasodilation in various circulations in the body, such as lung, gut and brain, not just the kidneys & coronaries) that decreases left and right ventricular afterload and complements the inotropic effect of the drug. Levosimendan has been investigated as a pharmacological intervention to prevent low cardiac output syndrome (LCOS) and reduce morbidity and mortality after cardiac surgery. The authors present a brief review of the literature and a case report

highlighting the potential benefits of the use of levosimendan in the preoperative conditioning of cardiac surgery patients.

Case Report

A 58-year-old Caucasian female patient was admitted to the intensive care unit for conditioning prior to a scheduled surgery consisting of a triple coronary artery bypass graft (CABG) with mitral reconstruction. On arrival, the patient was afebrile with a blood pressure of 87/36 mmHg and heart rate of 80/min (sinusal rhythm). Cardiac ultrasound showed significant left ventricular dilation (telediastolic diameter of 59 mm) associated with grade III mitral regurgitation. The patient was found to have an ejection fraction of 20% with antero-septo-apical and basal akinesia. There was also tricuspid regurgitation with pulmonary arterial systolic pressure evaluated at 43 mmHg. A 34 ml intra-aortic balloon pump (IABP) was placed, the hemoglobin and calcium levels were optimized and treatment with levosimendan was started at a dose of 0.10 µg/kg/min. The surgery was performed after 48 hours of supportive treatment. The postoperative course was characterized by a low cardiac output syndrome lasting 5 days, requiring vasoconstrictive and inotropic drugs (noradrenaline with a maximum dose of 0.11 µg/kg/min and adrenaline with a maximal dose of 0.17 µg/kg/min). The IABP was maintained at 1/1. Renal function improved, with creatinine decreasing from 1.15 mg/dl to 0.61 mg/dl. The patient left intensive care 13 days after admission without nosocomial infection or the need for renal replacement therapy (RRT). She was free of dyspnea at the time of discharge from hospital and was able to resume light sport activity (cycling and

walking). One year later, the patient's ejection fraction measured by echocardiography was found to be 35%. The continuing treatment consisted of sacubitril/valsartan 49/51mg once a day, bisoprolol 5 mg twice a day, apixaban 2.5 mg twice a day and atorvastatin 40 mg once a day.

Discussion

Preoperative conditioning for cardiac surgery includes a range of treatments aimed at the optimization of biological, hemodynamic, and infectious parameters. The use of IABP has shown a prophylactic benefit in CABG [1,2]. The association of levosimendan with IABP has to our knowledge not yet been evaluated. Controversy still exists in the literature regarding the use of levosimendan in cardiac surgery.

Levosimendan and Low Cardiac Output Syndrome

Low cardiac output syndrome (LCOS) is the result of a mismatch between oxygen delivery and its metabolic demand driven by myocardial dysfunction and circulatory failure. Following complex cardiac surgery requiring cardiopulmonary bypass (CPB), a decline in cardiac performance occurs with an increase in pulmonary and systemic afterload associated with a relative decrease in myocardial contractility [3]. Levosimendan is an inotropic calcium-sensitizing drug and a KATP channel opener and thus has myocardial protective properties. At the mitochondrial level, the opening of the KATP channel improves energy homeostasis and protects the heart from calcium overload and oxidative stress. At the coronary level, the opening of the KATP channel increases intracellular potassium resulting in coronary vasodilation, thereby improving blood flow

in ischemic areas with the net result of improving cardiac function [4]. Several randomized studies have shown benefit from the use of levosimendan when it was administered within 24 hours prior to surgery [5-7]. In these studies, patients had an ejection fraction of less than 40% and were conditioned for elective CABG surgery. All three studies showed a decrease in the incidence of LCOS. This benefit was also demonstrated in the LEVO-CTS study in a subgroup analysis of patients operated exclusively for CABG [8]. In the study by Levin et al, a decrease in complicated weaning from CPB (2.4% versus 9.6%; $p < 0.05$) was observed in patients receiving levosimendan [5].

Levosimendan and Renal Function

There is a decrease in the incidence of acute kidney injury (AKI) in patients on levosimendan. Levosimendan improves hemodynamics with an increase in cardiac output and a decrease in pressure in the right cardiac chambers which in turn decreases the pressure in the renal veins [4]. In addition, via its KATP channel-opening properties, Levosimendan induces vasodilation of the afferent arteriole, resulting in an increase in the glomerular filtration pressure. This is in contrast to dobutamine, which induces both afferent and efferent vasodilation [9]. In a study of 60 patients with LCOS randomized to receive either levosimendan or dobutamine, a significant improvement in renal function was observed in the levosimendan group (23% versus 3%, $p < 0.05$) [10]. Other studies have demonstrated this benefit, with a lower incidence of AKI on discharge from intensive care [11,12]. Several meta-analyses have shown a reduction in the need for RRT in patients with left ventricular dysfunction treated with levosimendan [12-14].

Levosimendan and Mortality

Several meta-analyses have shown a reduction in 30-day mortality in patients with preoperative left ventricular dysfunction and an ejection fraction below 40% [13,14]. However, three large multicenter randomized studies, the CHEETAH, LICORN and LEVO-CTS studies, have shown no benefit from the use of Levosimendan in terms of reduction in 30-day mortality [15,16,8]. The LEVO-CTS study showed only a trend in favor of levosimendan regarding 90-day mortality (4.7 vs placebo 7.1% $p = 0.12$) in patients undergoing isolated coronary artery bypass graft [8]. These studies included a broad spectrum of cardiac pathologies; however, when one considers only patients with coronary pathologies and an ejection fraction below 25%, there is a trend toward lower mortality with levosimendan [4]. A recent meta-analysis of 6 studies with a total of 590 patients demonstrated a benefit in 30-day mortality when levosimendan was compared with an active treatment rather than with placebo. These six studies comparing levosimendan with dobutamine, milrinone or IABP showed that levosimendan had lower mortality than other treatments (RR 0.32, 95 CI: 0.16 to 0.66, $p = 0.002$ and $I^2 = 0\%$) [17]. Some authors believe that the observed benefit may be linked to a lower exposure to exogenous catecholamines [18].

Conclusions

Large, randomized studies have not shown any mortality benefit of levosimendan compared to placebo. However, it seems that in ischemic pathology treated with CABG, patients with left ventricular dysfunction who receive levosimendan

may benefit in terms of mortality, low cardiac output syndrome and the need for renal replacement therapy when compared to classic dobutamine support strategies. The combined use of intra-aortic balloon pump and levosimendan deserves to be evaluated.

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