

Original Article

The Effectiveness of Levosimendan in Clinical Characteristics and Haemodynamic, in Patients Undergoing High-Risk Cardiac Surgery: A Systematic Review of Randomized, Clinical Trials

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Abstract

Aim: to evaluate the haemodynamic effects, perioperative and post-operative clinical characteristics of Levosimendan in in patients undergoing high-risk cardiac surgery.

Methods: The review of the literature was based on a keyword strategy and pre-determined inclusion and exclusion criteria. The citation and reference list of the eligible articles were also screened for potentially relevant articles. The outcomes were haemodynamic characteristics, length of ICU stay, and mortality rate. All RCTs with outcomes of interest were included

Results: In total, 9 studies met the criteria and were included in the systematic review. Six studies assessed the effectiveness of Levosimendan towards Cardiac Output and Clinical characteristics under CABG and three studies assessed the effectiveness of Levosimendan in other surgeries under cardiopulmonary bypass (CPB).

Seven out of the nine studies demonstrated significant improvement in the haemodynamic results in the Levosimendan group. The two studies also reported improvement but the result were not statistically significant probably due to the small sample size Methodologically the quality of most studies was moderate due to the small sample size, which might impact upon the significance of the findings. Furthermore, small sample sizes restricted the author to control for other demographic and clinical confounding factors. Only 4 out of the nine used power analysis calculation to estimate the required sample size to achieve statistical power. Only one paper performed a 4 blinded RCT with adequate to big sample size after power analysis

Conclusions: It is evident that Levosimendan has a significant impact on haemodynamics for patients in high risk surgery on both perioperative and post-operative period. No significant effect on mortality and morbidity rates.

Keywords: “clinical trials”; “Levosimendan”; “CABG”; “High Risk Cardiac Surgery” and “CPB”

Introduction

Levosimendan is a calcium sensitizer that enhances the contractile force of the myocardium by binding to troponin C without increasing intracellular calcium concentration at therapeutic doses. It does

not impair relaxation of intact paced guinea pig papillary muscles or of isolated failing human myocardium (Haikala et al. 1995; Haikala & Linden 1995). In addition, levosimendan exerts cardioprotective effects including coronary artery vasodilatation via

activation of triphosphate-regulated potassium channels at a dose that enhances myocardial contractility (Rump et al.; Kersten et al. 2000). Despite cardioplegic protection, cardiopulmonary bypass is associated with postoperative myocardial stunning, hypothermia, formation of microemboli, and systemic inflammatory response syndrome, all of which may prolong recovery from coronary artery bypass grafting (CABG) (Sohrabi et al. 2003).

We investigated the effects of Levosimendan in high risk cardiac surgery. The studies in this systematic review covered a range of diagnoses and pathophysiology as long they explored the effects of levosimendan on pre, post, and perioperative clinical results and haemodynamics

Material and methods

PUBMED electronic database was thoroughly searched from 2003 to date. The search was undertaken from November to December 2013 in order to identify the articles that met the inclusion and exclusion criteria and outcomes of interest.

The search strategy was identical for each of these electronic databases and was undertaken with the use of the following key words: “clinical trials”; “Levosimendan”; “CABG”; “High Risk Cardiac Surgery” and “CPB”

Inclusion/exclusion criteria

The inclusion criteria were as follows: (a) RCTs that use Levosimendan as a sole intervention or as an adjunct to another standard facilitator during a high risk cardiac surgery,

- (b) adult participants (>18+ years old),
- (c) monitored and compared haemodynamics and perioperative characteristics, and
- (d) written in English or Greek language.

Articles were excluded if:

- (a) the trials were in progress,
- (b) the trials were published in the form of dissertations, abstracts, single case studies, pilot studies, reviews or meta-analyses,
- (c) the trials did not focus on cardiothoracic surgery, and

(d) didn't include monitoring and contrast of haemodynamics between intervention and other groups.

Quality Appraisal

One of the methodological weaknesses identified was the small sample size with a range of papers (5 out 9) being small in both groups (no more than 20 in each group). The total number of patients participated in the studies was 595. Small sample sizes do not allow for in death statistical analysis i.e. control for confounding factors such as Age, Gender and other clinical characteristics

Moreover, Quality of Life has an effect on haemodynamics and perioperative characteristics as well as post operatives (i.e. ICU stay) and other clinical characteristics. Only Pasi Lahtinen et al (Lahtinen et al. 2011) confirmed the comparable QoL between control and Levosimendan group

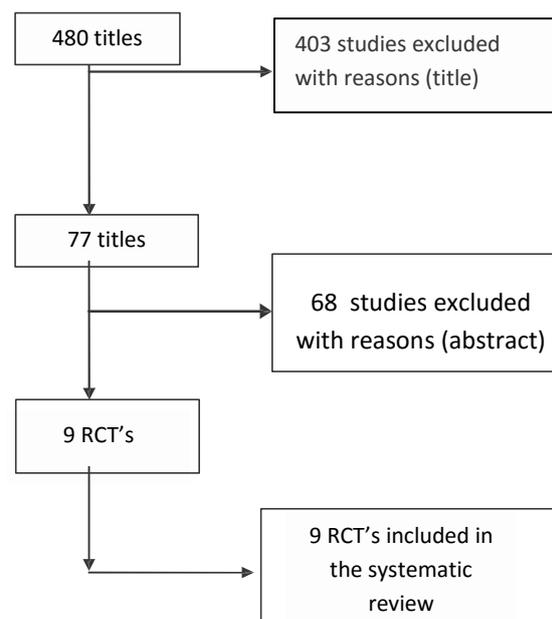


Figure 1 Flow Diagram of reviewed studies

A test on significant differences in the demographics of the patients in Intervention and Control groups was also contacted to avoid bias.

Confounding factors

All the studies did not control for confounding factors such as Gender and Age. It is documented (Nashef et al. 2002)

that although some indicate the control for *clinical setting confounding factors* such as total intravenous anesthesia (Husedzinović et al. 2005) two same surgeons performed all operations and one anesthesiologist was

responsible for the anesthesia and CPB (Tritapepe et al. 2009; Leppikangas et al. 2011). Nevertheless most of the studies didn't control clinical setting confounding factors.

Table 1 Levosimendan Dose and Methodological Quality considerations

Study	Levosimendan Group			Methodological quality		
	Loading dose (µg/Kg)	Maintenance dose (µg/Kg/min)	Deaths/Total Patients	Sample size calculation - Power Analysis	Control for Confounding Factors	Control for Clinical Setting Confounding factors
(Lahtinen et al. 2011)	24	0,2		Yes	No	No
(Lomivorotov et al. 2012)	12	0,1	4/90	No	No	No
(Eriksson et al. 2009)	12	0,2		Yes	No	No
(Leppikangas et al. 2011)	12	0,2	1/24	Yes	No	Yes
(Tritapepe et al. 2009)	24 as a slow i.v. bolus over a 10 min period		0/24	Yes	No	No
(Barisin et al. 2004)	24 & 12 (two Levo Groups+Control)		0/24	No	No	No
(Järvelä et al. 2008)	No Loading Dose	0,2	1/24	No	No	No
(Husedzinović et al. 2005)	12	0.2	0/24	No	No	No
(Momeni et al. 2011)	No Loading Dose	0,05 (Levo)- 0,04 (Milrinone)	0/24	No	No	No

Table 2 List of reviewed articles

Study	Study design	Objective	Intervention	Scales-tools/ Measurements	Population	Analysis - Software	Results
(Lahtinen et al. 2011)	Prospective, randomized, placebo-controlled clinical study	To investigate whether levosimendan diminishes the incidence of heart failure after cardiac surgery.	Two hundred patients assigned to undergo heart valve or combined heart valve and coronary artery bypass grafting surgery	Heart Failure index < 2,0 L/min/m ² or Failure to wean from CPB for 2hrs	n=99 in Levosimendan/ n=101 in Placebo	t tests, Fisher's exact test, Repeated Measures ANOVA, MannWhitney U, Kaplan - Meir Survival analysis, SPSS14.01	* reduced the incidence of heart failure * Improved mortality or morbidity was not demonstrated.
(Lomivorotov et al. 2012)	Prospective, randomized, clinical study	To test the hypothesis that levosimendan is more effective than intra-aortic balloon pump (IABP) support in cardiac surgical patients	3 Groups: Group A - prophylactic IABP. Group B- prophylactic IABP & levosimendan. Group C- levosimendan.	Hemodynamic and biochemical data	n=30 IAMP, n=30 IAMP+Levosimendan, n=30 Levosimendan only	ANOVA, Kruskal Wallies, Spearman Correlation, Fisher, Tukeys post hoc tests, Freeman-Halton, Sensitivity Specificity- Stata 11.2	*The infusion of levosimendan after anesthesia induction in cardiac surgical patients contributes to lower cardiac troponin I levels and improved hemodynamics compared with a preoperative IABP

(Eriksson et al. 2009)	Prospective, randomized, placebo-controlled double blind	Explore the effect of Levosimendan on weaning from early recovery after CPM	60 patients with 3-vessel coronary disease and left ventricular ejection fraction (LVEF) of less than 0.50	Proportion of patients successfully weaned from CPB by the first attempt. Haemodynamics Comparison	n = 30 in Levosimendan/ n = 30 in Placebo	ANOVA, chi square test, Cochran Mantel Haenszen, t-test, Fisher's exact test, Mann Whitney, ,Query Advisor 4.01	* Levosimendan significantly enhanced primary weaning from CPB compared with placebo * Need for additional Inotropic or mechanical therapy was reduced
(Leppikangas et al. 2011)	Prospective, randomized, placebo-controlled	Evaluate the haemodynamic effects of preoperative levosimendan in patients undergoing high-risk cardiac surgery.	Twenty-four patients levosimendan (12 µg bolus followed by an infusion of 0.2 µg kg(-1) min(-1)) or a placebo 24 h before surgery. left ventricular ejection fraction (LVEF) <50% or LV hypertrophy indicated by a wall thickness of >12 mm.	Statistically Significant differences between Control & Levosimendan group - SI, CI, HR, LVEF,ECW and effects across time (pre & postoperative	n = 12 in Levosimendan/ n = 12 in Placebo	RANOVA, t-test, Fisher's exact test, Mann Whitney, SPSS for Windows Ver 18.0	*Levosimendan improved haemodynamics compared with a placebo in patients undergoing high-risk cardiac surgery. * The concentrations of levosimendan's metabolites were higher compared with earlier studies using perioperative dosing.

(Tritapepe et al. 2009)	Prospective, Single-centre randomized, placebo-controlled trial, double blind	To investigate whether pharmacological pre-treatment with levosimendan reduces intensive care unit (ICU) length of stay	106 patients with Coronary Artery Disease undergoing elective myocardial revascularization under cardiopulmonary bypass.	Percentage of ICU stay, Higher tracheal intubation time and longitudinal assessment of postoperative clinical results	n=53 in Levosimendan/ n=53 in Placebo	chi square test, t-test, Fisher's exact test, Mann Whitney, ,SAS Release 9.1	*Levosimendan resulted in less myocardial injury, a reduction in tracheal intubation time, less requirement for inotropic support, and a shorter length of ICU stay.
(Barisin et al. 2004)	Randomized, placebo controlled, 4-times masked study	To test the hypothesis that levosimendan produced beneficial hemodynamic effects during and after off-pump CABG in patients with good preoperative left ventricular function	3 groups. Low dose (12µg/Kg) and High dose (24µg/Kg) and a Placebo group 31 patients undergoing OPCABG	Measurements of Haemodynamics Before, Just After, 5,20,50 min	n=10 in Placebo, n=11 in Low Dose, n=10 in High Dose	chi square test, t-test, Fisher's exact test, Mann Whitney, Kruskal Wallis test, Wilcoxon Rank test-SAS Release 6.12	*Both doses of levosimendan produced significant increased stroke volume and decreased systemic vascular resistance **Significant increases in cardiac output and left ventricular ejection fraction occurred in both Levosimendan Dose Groups *** Both Dose Groups decreased systemic vascular resistance **** Increase in stroke volume and decline in LVEF were dose related!

(Järvelä et al. 2008)	Prospective, randomized, placebo-controlled double blind	to test the hypothesis that levosimendan has beneficial effects on cardiac performance and reduces the need for other vasoactive medications	24 Patients with severe aortic stenosis (AS) and left ventricular (LV) hypertrophy scheduled for aortic valve surgery with or without coronary artery bypass graft surgery	Measurements of Haemodynamics before; after successful weaning from CPB bypass; after closing the sternum; postoperatively once every 3 hours	n=12 in Placebo, n=11 in Levosimendan group	chi square test, t-test, Fisher's exact test, Mann Whitney, Rep ANOVA-SPSS ver 12.0	* levosimendan may be useful in patients with severe AS and LV hypertrophy because it may prevent LV function from dropping to a critically low level postoperatively ** Cardiac output was slightly greater in the Levosimendan group, not statistically significant (may be due to sample size)
(Husedzino vić et al. 2005)	Prospective, randomized, placebo-controlled double blind	To determine if levosimendan could improve cardiac performance during off-pump coronary artery bypass grafting in patients with normal preoperative left ventricular function.	25 patients included - placebo (n=13) or 12 microg/kg loading dose of levosimendan (n=12) during a period of 15 minutes before the surgery	The heart rate, cardiac index, stroke volume index, and left ventricular ejection fraction were measured before and 10 and 60 minutes after the drug administration.	n=13 in Placebo, n=12 in Levosimendan group	Man Whitney, Wilcoxon Signed Rank Test and Friedman - SAS 6.12	*Cardiac index and left ventricular ejection fraction were significantly higher in Levosimendan group 10 and 60 minutes ** Stroke volume index was significantly higher at 10 minutes and higher but not significantly (p=0,66) at 60 minutes

(Momeni et al. 2011)	Prospective, randomized, placebo-controlled double blind	to compare Levosimendan to Milrinone as inotropic support	Patients were randomized in a double-blind fashion to a continuous infusion of either levosimendan at 0.05 µg/kg/min or milrinone at 0.4 µg/kg/min started at the onset of CPB. Epinephrine was started at 0.02 µg/kg/min after aortic cross-clamp release in both groups.	The hemodynamic and biochemical parameters were compared.	n=18 in Milrinone n=18 in Levosimendan group	chi square test, t-test, Fisher's exact test, Mann Whitney, Rep ANOVA-SPSS ver 12.0	* levosimendan is at least as efficacious as milrinone after corrective congenital cardiac surgery ** Lower troponin values (but not significant) *** Beneficial effects of Levosimendan were clear at 24 and 48 hours postoperatively
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Results

All trials were published between 2004 and 2012 and were conducted in different countries and different settings; University Hospitals, Private and University Clinics. All of the studies involved CABG surgery or off-Pump CAB or Cardiac Surgery under cardiopulmonary Bypass (CPB) and authors examined, among others, the effect of Levosimendan on Haemodynamics. The population examined involved patients with a range of Cardiac Diseases. Each study was assessed independently and data were collected on the clear wording of the purpose, design, size and characteristics of the sample, the methodology and the results. One of the methodological weaknesses identified was the small sample size with a range of papers (5 out of 9) being small in both groups (no more than 20 participants in each group) **Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε..** The total number of participants included in all the reviewed studies totaled to 595.

Preoperative Characteristics

Almost all papers investigate any significant differences in pre-operative clinical characteristics and/or haemodynamics. Moreover, a test on significant differences in the demographics of the patients in Intervention and Control groups was also conducted to avoid bias.

Levosimendan effect

The main purpose or related measurements of all RCTs was to evaluate the effectiveness of levosimendan in high risk cardiac patients. The majority of the studies (7/9) investigated the levosimendan effect with a Placebo Group. Two studies involved

Vladimir V. Lomirov et al (Lomirov et al. 2012) assigned patients with coronary artery disease and LVEF < 30%, randomly to 1 of 3 groups. Group A received a prophylactic IABP one day before surgery. Group B received a prophylactic IABP one day before surgery and a levosimendan infusion at a dose of 0.1 µg/kg/min with an initial bolus (12 µg/kg for 10 minutes) after anesthesia induction. Group C received a levosimendan infusion at a dose of 0.1

µg/kg/min with an initial bolus (12 µg/kg for 10 minutes) after anaesthesia induction. Hemodynamic and biochemical data and rate of complications were analyzed.

Pasi Lahtinen et al (Lahtinen et al. 2011) included a Quality of Life assessment preoperatively to avoid any bias in the results. In the study levosimendan infusion reduced the incidence of heart failure in cardiac surgery patients but was associated with arterial hypotension and increased requirement of vasopressor agents postoperatively. Improved mortality or morbidity was not demonstrated.

A different effect of Levosimendan was investigated by Heidi I. Ericson et al (Eriksson et al. 2009) where the main objective was to investigate whether Levosimendan could effectively facilitate weaning from cardiopulmonary bypass in patients undergoing CABG surgery. Most patients with uncompromised preoperative heart function can be weaned from cardiopulmonary bypass (CPB) without inotropic agents (Lahtinen et al. 2011). However, in patients with preoperatively impaired ventricular function, weaning failure without medical or mechanical support may be seen in up to 70% to 80% (Mentzer et al. 2007; Butterworth et al. 1993). The study concluded that Levosimendan enhanced primary weaning from CPB compared to control group, and need for additional inotropic was decreased as a result increased cardiac output in the intervention group.

Levosimendan effect on haemodynamics (recorded every hour for 24h and daily until postoperative day 4) and ICU stay was investigated in (Leppikangas et al. 2011). Levosimendan improved haemodynamics compared with a placebo in patients undergoing combined aortic valve and coronary bypass surgery. The concentrations of levosimendan's metabolites were higher compared with earlier studies using perioperative dosing. ICU stay was also lower in the Levosimendan group but not verified statistically and probably because the low sample size.

A big sample size (106) with patients undergoing elective CABG grafting

participated in the study by L. Tritapepe (Tritapepe et al. 2009). The study concluded that pre-treatment with levosimendan in patients undergoing surgical myocardial revascularization resulted in less myocardial injury, a reduction in tracheal intubation time, less requirement for inotropic support, and a shorter length of ICU stay.

The single 4 – times masked controlled study by Stjepan Barisin et al (Barisin et al. 2004) investigated the effect of Low (12µg/Kg) and High dose (24µg/Kg) of Levosimendan. They suggest that low-dose levosimendan could be preferable in this patient population undergoing OPCABG. Levosimendan offers a promising therapeutic option for management with optimal hemodynamic stability and enhances left ventricular performance during and after OPCABG in patients with good preoperative left ventricular function. The intervention groups produced good cardiac performance during and after the OPCABG procedure. The low-dose levosimendan used in this study demonstrated equivalent or a slightly better efficacy than the high-dose, because it produced stronger systolic response and lower peripheral vasodilatation.

The authors in (Järvelä et al. 2008) tested the hypothesis that Levosimendan has beneficial effects on cardiac performance and that the need for other vasoactive medications during and after cardiac surgery would be reduced by levosimendan in patients with severe aortic stenosis (AS) and left ventricular (LV) hypertrophy. Authors utilized all the necessary statistical tests to validate their findings. Nevertheless, due to the small sample size of the study several “positive” results for the Levosimendan group were not verified statistically i.e. Cardiac output, inotropic support.

Moreover, due to the non-optimal randomization of the patients, baseline cardiac performance was different in Control and Intervention group. Conclusions of the study were limited to the statement that the use of Levosimendan is a rational choice during and after cardiac surgery in patients with severe AS and LV hypertrophy.

98 patients participated in the study by Ino Husedzinovic et al (Husedzinović et al.

2005) where it concluded that levosimendan could improve cardiac performance during off-pump coronary artery bypass grafting in patients with normal preoperative left ventricular function. Significant decrease in the left ventricular EF was obtained after the administration of placebo (P=0.021). In comparison with the baseline measurement, the left ventricular EF was significantly lower 10 minutes (P=0.042) after the administration of placebo. In contrast to these findings, the left ventricular EF significantly increased in patients who received levosimendan (P=0.002). When compared with baseline values, this parameter was significantly higher 10 and 60 minutes (P=0.018 for all) after the administration of levosimendan.

In a different setting (comparison study) where levosimendan was compared to a milrinone, forty-one patients between 0 and 5 years old requiring inotropic support for corrective congenital heart surgery under cardiopulmonary bypass (CPB) were enrolled in (Momeni et al. 2011) by Mona Momeni et al. Thirty-six patients completed the study where a continuous infusion of either levosimendan or milrinone as inotropic support after corrective congenital cardiac surgery was used. The hemodynamic and biochemical parameters were compared. Although not significantly different, the troponin values in the levosimendan group were less at 1 hour and 4 hours postoperatively. This enabled them to conclude that Levosimendan is at least as efficacious as milrinone after corrective congenital cardiac surgery in neonates and infants.

Another comparison study (Lomivorotov et al. 2012) where Levosimendan was tested as better alternative to intra-aortic balloon pump (IAMP) found that haemodynamic were significantly improved and lower cardiac troponin levels were recorded. The patients were randomized into 3 groups – prophylactic IAMP only, prophylactic IAMP and a Levosimendan dose of 0.1 µg/Kg and - and group with only Levosimendan administration. The most widespread technique to manage the higher risk of complications and mortality after myocardial revascularizations, is to use an intra-aortic

balloon pump (IABP), particularly during the preoperative period (Maccioli et al. 1988). The positive effects of an IABP include afterload decreases, increases in coronary blood flow, and subendocardial perfusion (Santarpino et al. 2009). The authors of the study concluded that the use of Levosimendan is as effective as the use of IAMP

Conclusion

All the studies showed significant results of the use of Levosimendan irrespective of the surgery and pathophysiology. Haemodynamics are significantly improved and ICU stay and then need for Inotropic support are significantly reduced in most of the studies where adequate sample size allowed for statistically significant results.

In some studies the beneficial effect of Levosimendan were clear 1 or 2 days postoperatively.

Nevertheless it is event that Levosimendan produces good cardiac performance both peri-operatively and postoperatively. The effect of low dose and high dose was only investigated in one study and usually a loading dose of either 12 or 24 µg/Kg was administered. This leaves an area of investigation as to what dose is appropriate in what kind of surgery and disease

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