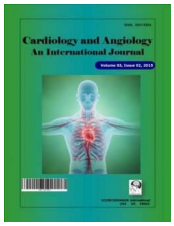

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Use of Levosimendan in Patients With Low Left Ventricular Ejection Fraction in Ordu/Turkey: Report of Experience with Mini Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AO and MY designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EG and SY managed the analyses of the study. Author KDT managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: To report the effect of prophylactic usage of levosimendan in patients with low left ventricular ejection fraction undergoing coronary artery bypass grafting (CABG).
Methods: We reported early results of 32 patients (26 male and 6 female; mean age 61.630 ± 9.653 years) who received preoperative levosimendan who underwent CABG with left ventricular ejection fraction (LVEF) of 35% or less between March 2014 and August 2016.

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Results: All patients achieved to wean from cardiopulmonary bypass. In only four patients there was a need for intraaortic baloon pump (12.5%). Mortality was in 4 patients (12.5%). And six months after the operation all patients (discharged from hospital) were alive.
Conclusion: Preoperatively administration of the long-acting inotrope levosimendan might be feasible and have a favourable safety profile in patients with severely reduced LVEF undergoing CABG. We suggest that levosimendan may be useful in high-risk CABG patients.

Keywords: Coronary artery bypass greft; low cardiac output syndrome; levosimendan.

1. INTRODUCTION

In patients undergoing cardiac surgery, postoperative low cardiac output syndrome (LCOS) has been shown to correlate with increased rates of organ failure and mortality. The main risk factor for LCOS is preoperative reduced left ventricular function [1].

For many years catecholamines have been the standard therapy, although they carry substantial risk for adverse cardiac and systemic effects, and mortality. Inotropic support is frequently initiated in the perioperative period to improve post-bypass ventricular function. But by increasing myocardial oxygen consumption they can cause cardiac ischaemia, with subsequent damage to hibernating but viable myocardium, and arrhythmias. And also the use of perioperative and postoperative inotropes has been found to be associated with increased mortality and major postoperative morbidity [2].

On the other hand, levosimendan has been shown to improve cardiac function with no imbalance in oxygen consumption, and to have protective effects in other organs [3].

Levosimendan is both a calcium sensitizer, and a potassium adenosine triphosphate(ATP)-dependent channel opener. It enhances myocardial contractility without increasing the concentration of intracellular calcium, leads to vasodilation, which reduces left ventricular afterload and improves blood flow to vital organs. Levosimendan may facilitate weaning from cardiopulmonary bypass (CPB). It enhances both systolic and diastolic left and right ventricular performance [4].

Patients with low preoperative LVEF <35%, high-risk patients (emergency operation, decompensated heart failure), weaning failure from CPB, scheduled for mechanical assist device (intra- aortic balloon pump) (IABP)/left ventricular assist device), or post-operative LCOS are candidates to receive levosimendan in cardiac surgery [4].

To improve peri and post-operative haemodynamics and to reduce morbidity and hospital stay is the main aims of levosimendan usage. The use of levosimendan before surgery improves the cardiac output, stabilizes the patient, reverses the organ failure and exerts cardioprotective effect.

In patients with a LVEF estimated as less than 35% on transthoracic echocardiography at our clinic are considered for pre-operative levosimendan infusion for 12 hours prior to surgery. The aim of this study is to describe the effect of levosimendan (with loading dose) on hemodynamics, complications and mortality in cardiac surgery patients.

2. MATERIALS AND METHODS

Between March 2014 and August 2016, patients with LVEF ≤35% underwent elective CABG received levosimendan before surgery at our hospital were analyzed. Because of the retrospective structure of this study, permission from the ethics committee was not necessary.

The main criteria for inclusion were isolated coronary artery disease, impaired LVEF ≤35% evaluated with left ventricular echocardiography. The main exclusion criteria were redo CABG operation, indication for any cardiac valve operation, severe chronic obstructive pulmonary disease, severe renal insufficiency and emergent surgery.

Data were collected retrospectively via the electronic clinical information system. The data collected included age, sex, intensive care unit (ICU) and hospital length of stay, ICU, and in-hospital and 6 month mortality.

Hemodynamic data including mean arterial pressure, heart rate, arterial lactate, base excess

and rates of inotrope were recorded. Adverse events were recorded. Here, typically, patients have been admitted ICU the night before surgery and received 12 hours of therapy prior to surgery.

Levosimendan (Simdax; Abbott, Luxemburg, Luxemburg) infusion was started intravenously 12 hours before the operation at a dose of 0.1 microgram/kg/ min with a loading dose of 6 µg/kg in the ICU through a central venous line; hemodynamics were closely monitored [5].

In all patients conventional median sternotomy was performed. CPB was initiated after cannulation of the right atrium and ascending aorta. Distal and proximal anastomoses were constructed during a single period of aortic cross-clamping. After chest closure, each patient was transferred to ICU under sedation, intubation and mechanical ventilation.

Patients were transferred from the ICU to the wards when they met the following criteria: stable hemodynamics without inotropic and vasoactive support, urine output 0.5 mL/kg/h, and minimal drainage.

2.1 Statistical Analysis

For descriptive statistics for Windows (SPSS Inc., Chicago, IL, USA) SPSS version 17.0 software package was used. In this study continuous variables was shown as mean ± standard deviation and categorical variables were shown as the frequency and percentages.

3. RESULTS

Table 1 shows the distrubition of the descriptive characterics of patients.

Their mean age was 61.630 ± 9.653 years, and twenty six of the patients were (81.2%) male and 6 (18,8 %) of them were female. The mean value of euroSCORE II was 6.7.

Mortality was in 4 patients (12.5%). Three of them died in postoperative first, second and third day respectively because of LCOS and the other on postoperative fifth day because of cerebrovascular disease (CVD).

Fourteen patients had no complication, 12 patients (37.5%) had atrial fibrillation, 1 patient (3.1%) had CVD, 2 patients had bleeding revision, 3 patients (9,3%) had LCOS.

Table 1. The distribution of descriptive characteristics

Tables	Groups	Frequency(n)	Percentage (%)
Gender	M	26	81.2
	F	6	18.8
	Total	32	100.0
Mortality	No	28	87.5
	Yes	4	12.5
	Total	32	100.0
Complication	No	14	43.8
	AF	12	37.5
	CVD	1	3.1
	Bleeding Revision	2	6,2
	LCOS	3	9.3
	Total	32	100.0
Operation	CABGx3	12	37.5
	CABGx4	14	43.7
	CABGx5	6	18.8
	Total	32	100.0
IABP	No	28	87.5
	Yes	4	12.5
	Total	32	100.0
Mortality in 6 months	No	28	100
	Yes	0	0
	Total	28	100.0

AF: atrial fibrilliation; CABG: coronary artery bypass greft; CVA: cerebrovascular disease; F: female; IABP: Intraaotic balloon pump; LCOS: low cardiac output syndrom; M:male

Twelve (37.5%) patients had CABG with 3 grafts (CABGX3), 14 (43.7%) patients had CABG with 4 grafts (CABGX4), 6 (18.8%) patients had CABG with 5 grafts (CABGX5).

In only four patients there was a need for intraaortic baloon pump (IABP) (12.5%).

And six months after the operation all patients (discharged from hospital) were alive.

Table 2 shows the average values of the descriptive characterics of patients.

Mean age of the patients was 61.6 ± 9.6, preoperative EF was 29.3 ± 3.5%.

The mean cross clamp time and cardiopulmonary bypass time were 80.880 ± 26.414 and 99.6 ± 34.0 minutes respectively.

The mean time for extubation 21.7 ± 20.7 hours, the length of stay in ICU and at hospital were 2.5 ± 0.9 and 7.3 ± 3.4 days respectively.

There are 20 patients in New York Heart Association (NYHA) class III and 12 patients in class IV. All patients received noradrenalin between doses of 0,050- 0,075 µg/kg/min during weaning from cardiopulmonary bypass (Table 3). In 29 patients without LCOS there was no need for another inotropic agent. The patients with LCOS received adrenaline and noradrenaline between the doses of 0.100- 0.175 µg/kg/min.

4. DISCUSSION

Levosimendan is an inotropic agent thought to be effective in the prevention and treatment of the LCOS after cardiac surgery.

Levosimendan increases the Ca+2 response to myofilament by binding to cardiac troponin C and myocardial contraction increases without increasing myocardial oxygen demand [6]. Levosimendan was shown to open the mitochondrial ATP-dependent potassium channels in myocytes and vascular smooth muscle cells, which causes vasodilatation and also responsible for the potential pre-conditioning effect of the drug [7]. It decreases both preload and afterload, increases coronary and other organs blood flows [8].

These are the differences of levosimendan from other inotropic agents and the reason why it is considered as a good choice in high-risk patients undergoing cardiac surgery [9]. Levosimendan can be administered before operation, before, during, or after CPB, or in the ICU after the surgery.

Table 2. The average values of descriptive characteristics

	N	Mean	Sd	Min.	Max.
Age	32	61.6	9.6	45.0	84.0
Preoperative EF	32	29.3	3.5	25.0	35.0
Extubation Time (Hour)	32	21.7	20.7	8.0	72.0
XCT (minute)	32	80.8	26.4	41.0	123.0
CPB (minute)	32	99.6	34.0	62.0	171.0
Length of ICU stay(day)	32	2.5	0.9	2.0	5.0
Discharge From Hospital (day)	32	7.3	3.4	0.0	14.0

CPB: cardiovascular bypass time; EF: ejection fraction; ICU: intensive care unit; XCT: cross clemp time

Table 3. Patients' status

Gender	**M: 26**	**F: 6**
NYHA	Class III: 20	Class IV: 12
Levosimendan (preoperative and postoperative)	6 µg/kg loading dose (10 minutes)	0.1 µg/kg/min continuous infusion (24 hours)
Noradrenalin (postoperative)	0,050- 0,075 µg/kg/min İn 29 patients	0.100- 0.175 µg/kg/min in patients with LCOS
Adrenaline (postoperative)	------	0.100- 0.175 µg/kg/min in patients with LCOS

F: female; M:male; LCOS: low cardiac output syndrom; NYHA: New York Heart Association Functional Classification

Levosimendan is administered via continuous intravenous infusion following a weight based loading dose. The administration of levosimendan preoperatively requires an adequately monitored environment for patients; volume optimization is essential, a bolus should not be administered if the systolic blood pressure is under 100 mmHg.

It has a short half-life about 1.5 hours but its active metabolite (OR-1896) has approximately 80 hours. Because of the long half-life of the active metabolite, its effects last till up to 7 to 9 days after discontinuation of a 24-hour infusion [10].

Many patients with high rate of comorbidities need cardiac surgery, and have increased risk of perioperative mortality. Especially patients with severely decreased LVEF have a significantly increased risk of mortality. Some patients need pharmacologic assist to overcome the myocardial stunning and to reach hemodynamic stability.

LCOS and complicated weaning from CPB may lead to myocardial distension and damage, end-organ failure due to impaired perfusion, neurologic complications, prolonged operation times, longer stay in the ICU, prolonged mechanical ventilation, and increased risk of infection, sepsis and increased mortality [5].

The ratio of patients who require positive inotropic support after CPB is 32.4%. When the patient had preoperative EF <30% this ratio is inceased to 92% [11]. In patients with poor ventricular function, weaning failure from CPB without medical and/or mechanical support may be seen in up to 70%- 80% [12].

The cardioprotective strategies for improving short term and long-term outcomes are intra-aortic balloon counterpulsation, assist devices, avoidance of catecholamine-induced cardiotoxicity and myocardial preconditioning [13].

Patients who fail to be weaned from CPB can benefit from levosimendan. Levosimendan improves myocardial contractility without increasing myocardial oxygen demand and causes coronary and peripheral vasodilatation, helps to achieve an optimal cardiac index [14]. Levosimendan has an influence on mitochondrial potassium channels, and may decrease the incidence of postoperative organ failure [15].

Clinical studies show that in patients, undergoing cardiac surgery levosimendan effectively improves general and pulmonary haemodynamics, shortens the length of stay in the ICU and hospital, reduces complications.

Leppikangas et al. reported that levosimendan improved haemodynamics during the 4 day postoperative period, when infused a day before surgery [16]. Since we do not have a control group in our study, it is not possible for us to make comparison because we routinely apply levosimendan to all patients with low EF in our clinic. On the other hand, our patients did not force for weaning from CPB.

In a retrospective analysis Lahtinen et al. reported that post- operative bleeding was 31% greater amongst levosimendan receiving patients [17]. There was only two patients that had surgical re-exploration for bleeding in our study.

Maharay et al. included 729 patients from 17 studies in their meta-analysis. Levosimendan was associated with mortality reduction after coronary revascularization, significantly improved cardiac index, shortened ICU stay, and reduced rate of atrial fibrillation and magnitude of postoperative troponin I release [18]. Hernandez et al. included 654 patients from 13 studies in their analysis. Levosimendan was associated with a significant reduction in postoperative mortality [19].

Niu et al. reported included a lower incidence of acute kidney injury [20]. Lim et al. reported that levosimendan significantly reduced early patient mortality in a total of 965 patients in 14 studies. And also, postoperative acute renal failure (ARF) was less frequent, and ICU stay was shorter in the levosimendan group [21]. There was no acute renal failure in our study. Twelve patients had atrial fibrillation.

Zhou et al. published a meta-analysis of 13 trials with a total of 1345 study patients. Levosimendan was statistically superior in incidence of postoperative ARF, duration of mechanical ventilation, ICU stay, and post-operative mortality [22]. In our study duration of mechanical ventilation was 21 hours meanly.

Rajek et al reported the use of levosimendan in patients with congestive heart failure and a preoperative LVEF of 19±5% undergoing elective cardiac surgery [23]. There was a reduction in the need for IABP, catecholamine requirements and the duration of ICU stay.

In our study mortality was in 4 patients (12.5%). Three of them died in postoperative first, second and third day because of LCOS and the other on postoperative fifth day because of CVD. And in only four patients there was a need for IABP.

Tritapepe et al. observed that levosimendan allows the avoidance of high doses of conventional inotropes [24]. De Hert et al. reported that levosimendan produces beneficial hemodynamic effects in patients with pre-operative LV dysfunction (LVEF <30%) who required inotropic support after CPB [11]. In our study all patients received noradrenaline after CPB.

Levin et al. reported that preoperative levosimendan infusion reduced mortality and the risk for postoperative LCOS in contrast to placebo in patients with severe left ventricular dysfunction [25]. LCOS was seen in three of our patients and all of them died.

In contrast Mehta et al. reported in a randomized, placebo-controlled, newest study that, levosimendan was not associated with a lower rate of the composite of death, renal-replacement therapy, perioperative myocardial infarction, and use of a mechanical cardiac assist device than placebo [26]. In their study any adverse event was seen in 55.6%, 3 months-death in 4.7% and LCOS in 18.2%. In our study these rates are 56.2%, 12.5% and 9.3% respectively. The reason for the greater numbers may be the small numbers of total patients.

The typical dosage of intravenous levosimendan as used in our clinic is 6 µg/kg loading dose over 10 minutes followed by 0.1 µg/kg/min continuous infusion. Nausea, dizziness, headache and hypotension are the most common side effects of levosimendan [27]. Other side effects are arrhythmias, atrial fibrillation, extrasystoles, atrial or ventricular tachycardia, myocardial strain or ischemia, hypokalemia, or preexisting severe nausea. Most of the reported adverse effects of levosimendan were related to the bolus loading dose.

Levosimendan infusion was tolerated well in our patients. Only in four patients we stopped the loading dose because of hypotension and then continued with maintenance dose.

Table 4. Studies with levosimendan

	Number of patients	Type of the study	Results
Leppikangas	24	prospective randomized	improved haemodynamics
Lahtinen	200	Prospective, randomised/vs. placebo	increased risk of postoperative bleeding
Maharay	729	meta-analysis	mortality reduction, improvements in length of ICU stay ,in the rate of atrial fibrillation and troponin I levels
Hernandez	13 studies	meta-analysis	reduction in mortality
Niu	529	meta-analysis	reduced renal injury
Lim	14 studies	meta-analysis	reduced early mortality, improves clinical outcomes
Zhou	1345	meta-analysis	reduced acute kidney injury and postoperative mortality
Rajek	8	prospective	Reduced catecholamine requirements and decreased critical care duration
Tritapepe	24	Pilot study	evidence of less myocardial damage
De Hert	30	randomised	Reduced inotropic drug, shorter tracheal intubation
Levin	252	Randomised/vs. placebo	lower mortality, decreased risk for LCOS, reduced requirement for inotropes
Mehta	849	randomized, placebo-controlled	Not reduced death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device

5. STUDY LIMITATIONS

The main limitation of our study was the relatively small number of patients and absence of the control group. This is because we use levosimendan in our patients with low EF routinly. These results show that preoperatively levosimendan treatment is feasible even with bolus, has a safety profile and may help to prevent low cardiac output syndrome. Patients did not receive only levosimendan and the observed effects are not only due to this drug. More prospective, controlled randomized clinical trials with larger number of patients are needed in the investigation of levosimendan and its role in patients with poor LV function after cardiac surgery.

6. CONCLUSION

This study suggests that introduction of levosimendan at a dose of 0,1 µg/kg /min with a loading dose of 6 µg/kg in the ICU, in a patient group undergoing cardiac surgery was well tolerated.

Our study shows that the elective preoperative administration of levosimendan especially 12 hours before the operation might help patient to wean from CPB, might decrease need for inotropic agents and IABP support.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable. Because of the retrospective structure of this study, permission from the ethics committee was not necessary.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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