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Research Article / Araştırma

# Levosimendan Use After Cardiac Surgery: A Single-Center Experience

## *Kalp Cerrahisi Sonrası Levosimendan Kullanımı: Tek Merkez Deneyimi*

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## ABSTRACT

**Objectives:** Low cardiac output syndrome (LCOS) after cardiac surgery is associated with high mortality. Levosimendan is beneficial in the treatment of LCOS. The aim of this study is to describe the results of levosimendan in our hospital, considering the discussions in the literature.

**Methods:** This was a retrospective analysis of data from patients receiving levosimendan postoperatively at a tertiary cardiac surgery center between November 2019 and February 2021. In the intensive care unit, each patient was started on levosimendan at a loading dose of 12 mcg/kg/10 min, followed by a maintenance dose of 0.1 mcg/kg/min for 24 h. The dose was halved when hypotension developed.

**Results:** The mean age of the patients in the study was 55.87±12.322 years. Five (33.3%) of them were female. Ten of them had hypertension, eight had diabetes mellitus, two had chronic obstructive pulmonary disease, and two had chronic renal failure. Postoperatively, we had 3 mortalities (20%). Mean duration of hospital stay was 29.4±18.715 days and mean duration of intensive care stay was 11.27±11.985 days. Seven patients had acute kidney injury following the surgery, whereas only two of them needed renal replacement therapy.

**Conclusion:** Levosimendan is an agent that can be successfully used to treat patients with LCOS. It can be used before surgery in patients with higher risk before LCOS is developed.

**Keywords:** Cardiac surgery, levosimendan, low cardiac output syndrome

## ÖZ

**Amaç:** Kardiyak cerrahi sonrası düşük kardiyak debi sendromu yüksek mortalite ile ilişkilidir. Levosimendan, düşük kalp debisi sendromunun tedavisinde faydalıdır. Bu çalışmanın amacı, literatürdeki tartışmaları göz önünde bulundurarak hastanemizde levosimendan sonuçlarını betimlemektir.

**Yöntem:** Bu çalışma, Kasım 2019-Şubat 2021 tarihleri arasında bir üçüncü basamak kalp cerrahisi merkezinde ameliyat sonrası levosimendan alan hastalardan elde edilen verilerin retrospektif bir analizidir. Yoğun bakım ünitesinde her hastaya levosimendan 12 mcg/kg'dan 10 dakikalık bir yükleme dozuyla başlandı, 24 saat boyunca 0,1 mcg/kg/dakikalık idame dozuyla devam edildi. Hipotansiyon geliştiğinde doz yarıya indirildi.

**Bulgular:** Çalışmaya alınan hastaların yaş ortalaması 55,87±12,322 yıl idi. Bunların 5'i (%33,3) kadındı. Hastaların 10'unun hipertansiyonu, sekizinin diabetes mellitusu, ikisinin kronik obstrüktif akciğer hastalığı ve ikisinin de kronik böbrek yetmezliği vardı. Ameliyat sonrası 3 (%20) mortalite oldu. Ortalama hastanede kalış süresi 29,4±18,715 gün, ortalama yoğun bakımda kalış süresi 11,27±11,985 gün idi. Ameliyat sonrası yedi hastada akut böbrek hasarı oluşurken, bunlardan sadece ikisinde renal replasman tedavisi gerekti.

**Sonuç:** Levosimendan, düşük kalp debisi sendromu olan hastaların tedavisinde başarıyla kullanılabilen bir ajandır. Düşük kardiyak output sendromu gelişmeden önce yüksek riskli hastalarda cerrahi öncesi kullanılabilir.

**Anahtar sözcükler:** Düşük kardiyak debi sendromu, levosimendan, kardiyak cerrahi

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## Introduction

Low cardiac output syndrome (LCOS) after cardiac surgery is associated with high mortality.[1] LCOS is mostly managed with inotropic agents and partially with mechanical cardiac assist devices.[2] Inotropic therapy includes the use of beta-adrenergic agonists and phosphodiesterase inhibitors. However, routinely used inotropic agents can cause serious side effects. Studies have shown that the use of inotropes leads to an increased risk of mortality, stroke, arrhythmia, and the need for renal replacement therapy.[3]

Levosimendan is a calcium-sensitizing and adenosine triphosphate-sensitive potassium channel opening inodilator.[4] Some studies showing that levosimendan is beneficial in the treatment of LCOS without increasing myocardial oxygen consumption in the post-operative period.[5-7] However, two recently published placebo-controlled, randomized, and clinical trials have shown that levosimendan has no beneficial effects on 30-day mortality after cardiac surgery when applied perioperatively.[8,9]

The aim of this study is to describe the results of levosimendan in our hospital, considering the discussions in the literature.

## Methods

This was a retrospective analysis of data from patients receiving levosimendan postoperatively at a tertiary cardiac surgery center between November 2019 and February 2021. Patients treated with levosimendan were identified using the hospital's database, and then their medical records were reviewed. Our exclusion criteria were as follows: Patients younger than 18 years of age and patients receiving levosimendan treatment in the pre-operative period.

Age, gender, heart failure grade according to New York heart association (NYHA) classification, EuroScore (European system for cardiac operative risk evaluation) II, presence of comorbidity, history of cardiac reoperation, and echocardiographic findings at first admission were evaluated in the study population. The operation data included which operation was performed, cardiopulmonary bypass (CPB) time, cross-clamp time, which type of cardioplegia was used, and the need for inotropes when exiting CPB. Parameters used to describe patients' outcomes included: Inotrop score, echocardiographic changes, need for renal replacement therapy, development of arrhythmia, development of sepsis, pneumonia, development of shock, intensive care and hospital stay, use of extra corporeal membrane oxygenation (ECMO) and intra-aortic balloon pump (IABP), and early mortality.

Invasive arterial blood pressure, central venous pressure, and ECG are routinely monitored in all the patients following the surgery in the intensive care unit. No additional monitorizations were made after the initiation of levosimendan. Patients were followed up through transthoracic echocardiography. The decision to use levosimendan in patients is made by the surgical team of the patients and there is no routine protocol for the use of levosimendan in postoperative patients in our hospital. It is preferred for patients whose intensive care unit stay is prolonged due to LCOS, inotropic support cannot be decreased, and EF values are decreased compared to baseline in post-operative echocardiographic examinations. In patients, levosimendan was not used preoperatively for protection, but was planned to contribute positively to the healing process in the post-operative period. In the intensive care unit, each patient was started on levosimendan at a loading dose of 12 mcg/kg/10 min, followed by a maintenance dose of 0.1 mcg/kg/min for 24 h. The dose was halved when hypotension developed. Hypotension was seen in 3 patients (20%). The dose was halved until the mean arterial pressure was >65 mm-Hg. Then, the drug was brought back to the normal dose and the treatment was completed in 24 h.

Statistical analyzes were performed using R version 4.0.3 (R Foundation for Statistical Computing). Kolmogorov–Smirnov test was used to determine the abnormal distribution. Normally distributed continuous data were presented as mean and standard deviation (SD). Abnormally distributed continuous data were presented as median, first, and third quartiles (Q1-Q3). Categorical data were presented as number of patients and ratio.

This retrospective study was approved by the Local Ethics Committee (with the folder number: 2020-51). The study was conducted according to the principles of the Declaration of Helsinki.

## Results

The mean age of the patients in the study was 55.87±12.322 years. Five (33.3%) of them were female. Ten of them had hypertension, eight had diabetes mellitus, two had chronic obstructive pulmonary disease, and two had chronic renal failure.

Three of the patients had pre-operative atrial fibrillation. Mean left ventricular ejection fraction was 35.13±12.135%. Most of the patients (66.7%) had NYHA Class 3-4 symptoms. Pre-operative demographic and clinical data are summarized in Table 1.

Between 2019 and 2021, 15 patients needed levosimendan therapy after surgery. Three of them had undergone isolated coronary artery bypass grafting (CABG). Four of them had isolated valvular surgery and eight of them had undergone combined valvular surgery+CABG. Mean

**Table 1.** Pre-operative demographical and clinical characteristics of the patients

| Demographical and clinical data | n | % | Mean±SD and median (Q1-Q3) |
|---|---|---|---|
| Age | | | 55.87±12.322 |
| Sex | | | |
| Female | 5 | 33.3 | |
| Male | 10 | 66.7 | |
| HT | 10 | 66.6 | |
| DM | 8 | 53.3 | |
| COPD | 2 | 13.3 | |
| Renal failure | 2 | 13.3 | |
| Pre-operative atrial fibrillation | 3 | 20 | |
| LVEF | | | 30 (42-27) |
| PAP | | | 35 (30-40) |
| NYHA Class 3-4 | 10 | 66.6 | |
| Cardiac reoperation | | 6.7 | |
| EuroSCORE II | 3.40 | 2.681 | |
| CRE | | | 0.88±0.20 |
| GFR | | | 90.6±20.7 |

SD: Standart deviation; HT: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricular ejection fraction; PAP: Pulmonary artery pressure; NYHA: New york heart association; CRE: Creatine; GFR: Glomerular filtration rate.

**Table 2.** Distribution of operation types and comparison of the operative data

| Operation type | n | % | Mean±SD and median (Q1-Q3) |
|---|---|---|---|
| Isolated CABG | 3 | 20 | |
| Isolated valve surgery | 4 | 26.7 | |
| CABG+valvular | 8 | 53.3 | |
| CPB Time, min | | | 138 (113-173) |
| CC time, min | | | 76 (72-99) |
| Warm blood cardioplegia | 8 | 53.3 | |
| Del nido cardioplegia | 7 | 46.7 | |
| Reexploration | 3 | 20 | |

SD: Standart deviation; CABG: Coronary artery bypass grafting; CPB: Cardiopulmonary bypass; CC: Cross clamp.

**Table 3.** Comparison of the post-operative data

| Postoperative data | n | % | Mean±SD and median (Q1-Q3) |
|---|---|---|---|
| Hospital mortality | 3 | 20 | |
| ICU stay (days) | | | 8 (5-10) |
| Hospital stay (days) | | | 22 (16-33) |
| Post-operative LVEF | | | 25 (23-30) |
| Post-operative PAP | | | 35 (30-50) |
| Post-operative AF | 7 | 46.7 | |
| AKI | 7 | 46.7 | |
| RRT | 2 | 13.3 | |
| Peak CRE | | | 1.25 (0.88-2.17) |
| Peak GFR | | | 59.05±20.658 |
| Pulmonary complications | 1 | 6.7 | |
| Inotrope use | 15 | 100 | |
| Inotrope score | | | 12 (6-20) |
| Milrinone use | 1 | 6.7 | |
| IABP | 0 | 0 | |
| ECMO | 1 | 6.7 | |

SD: Standart deviation; ICU: Intensive care unit; LVEF: Left ventricular ejection fraction; PAP: Pulmonary artery pressure; AF: Atrial fibrillation; AKI: Acute kidney injury; RRT: Renal replacement therapy; CRE: Creatine; GFR: Glomerular filtration rate; IABP: Intra-aortic balloon pump; ECMO: Extra corporeal membrane oxygenation.

cross clamping time was 84.53±47.199 min. Mean CPB time was 148.26±67.858 min (Table 2).

Postoperatively, we had 3 mortalities (20%). Mean duration of hospital stay was 29.4±18.715 days and mean duration of intensive care stay was 11.27±11.985 days. Seven patients had acute kidney injury following the surgery, whereas only two of them needed renal replacement therapy (Table 3). Only one patient needed ECMO. This was a patient with a low ejection fraction preoperatively. Mitral valve replacement and tricuspid ring annuloplasty were performed. The patient was extubated on the post-operative 1st day. However, LCOS was developed. Echocardiography revealed an EF of 15-20%. ECMO support was initiated. Levosimendan was administered to ease the weaning process. Unfortunately, the patient was lost. Remaining 12 patients were successfully discharged from the hospital.

## Discussion

Over the years, cardiac surgical procedures, despite the increase in complexity, can be successfully done with minimum complication rates. LCOS is one of the most common and most serious complication associated with mortality and morbidity.[1] Mortality rates can be as high as 38%.[10] In addition to the increased mortality rates, morbidities also increase such as neurological problems, acute kidney injury, pulmonary complications, and need for reexploration.[11] Recent meta-analyses showed that use of levosimendan in this patient group reduces mortality, LCOS and associated complications.[12] In our study, our mortality rate was up to 20% slightly better than the LCOS mortality rates reported in the literature. Most of our patients were successfully discharged from the hospital after levosimendan treatment.

Recent studies also showed that patients with systolic dysfunction undergoing CABG have higher probability to suffer LCOS.[13] It is also showed that levosimendan admin-

istration before the surgery may improve the outcomes of the surgery.[13] It is also shown by Xie et al.[14] that even right after an acute myocardial infarction, levosimendan can prevent cardiac myocyte apoptosis in animal models. There is also a study conducted by Kaddoura et al.[15] showing better result even in patients with extracorporeal membrane oxygenation postoperatively. In our study, we administered levosimendan only after the surgery with the patients suffering from LCOS. These studies create a new horizon for what is known on the subject with further investigations to make.

Levosimendan has some secondary advantages besides improving the cardiac functions. AKI is a common complication of cardiac surgery and LCOS.[16] It is shown that levosimendan improves the renal functions through increasing the cardiac output and preglomerular vasodilatation. It is also claimed that need for renal replacement therapy is also decreases with levosimendan.[12] We had seven patients with AKI, two needed renal replacement therapy. This is almost half of our population. The probable reason for that was mostly due to the late administration of levosimendan after the patients developed LCOS. Furthermore, the positive effects of levosimendan are seen several hours after its administration;[9] therefore, we have more AKI than expected. On the other hand, most of them were successfully treated without need for permanent dialysis.

Our study has several limitations. First, the retrospective nature of the study is our major limitation on the matter. We have a limited number of patients. We conducted this study only because this is the first series reported from Turkey to the best of our knowledge. To have better results and to make comparisons we need randomized, controlled, and multi-centered studies to achieve better results.

Levosimendan is an agent that can be successfully used to treat patients with LCOS. It can be used before surgery in patients with higher risk before LCOS is developed. It will help the surgeons to better cope with LCOS after cardiac surgery.

### Disclosures

**Ethics Committee Approval:** The study was approved by The Istanbul University of Health Sciences Mehmet Akif Ersoy Thoracic and Cardioavscular Surgery Training and Research Hospital Clinical Research Ethics Committee (Date: 29/04/2022, No: 2020-51).

**Informed Consent:** Written informed consent was obtained from all patients.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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