Perioperative Use of Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery on Cardiopulmonary Bypass

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Abstract

Background: Patients undergoing cardiac surgery are becoming older and with greater comorbidities, carrying an increased risk for perioperative complications which result in higher mortality and higher costs for the health care service.

Objective: Our study is randomized, double-blind, placebo-controlled, multicenter clinical study to evaluate the efficacy of levosimendan given preoperatively in high-risk patients with LVEF ≤35% undergoing cardiac surgery on CPB.

Patients and methods: This study was carried out in (Cardiothoracic Department National Heart Institute, Al Hussin hospital, Air Forced Specialized hospital, Saudi Jerman hospital). Approximately 60 patients treated with study drug will be enrolled, the study population is drawn from patients with an LVEF ≤35% scheduled to undergo cardiac surgery with planned CPB.

Results: Our results showed that the relative risk for postoperative mortality at 60 days was reduced by 10% in the levosimendan group when compared with the control group [4of 30 (13%) in the levosimendan group vs 7of 30 (23%) in the placebo group] with p value=0.5 however the Incidence of 30-day out-of-hospital complications was not statistically difference between the two groups. In the levosimendan group, no significant reduction in the rate of renal replacement therapy was observed [7 of 30 (23.3%) in the levosimendan group vs 8 of 30 (26.7%) in the placebo group].

Conclusion: Levosimendan is safe and well tolerated in patients undergoing cardiac surgery with cardiopulmonary bypass who have low LVEF and are at risk of the development of postoperative LCOS.

Keywords: Levosimendan, Left Ventricular Systolic Dysfunction, Cardiac Surgery, Cardiopulmonary Bypass

1. Introduction

Low cardiac output syndrome (LCOS) is generally more common among patients with impaired left ventricular function, and is managed with inotropic agents and, eventually, mechanical support such as intra-aortic balloon pump, extracorporeal membrane oxygenator or ventricular assist devices. Although recent advances in pharmacologic and mechanical treatments, short-term mortality risk for patients with LCOS remains up to 15 times higher compared to an uneventful post-operative course1.

Most of the available inotropic agents have detrimental side effect or have a poor safety profile, thus exposing the patient to treatment-related risks and complications, the prevention and the effective treatment of LCOS is one of the pivotal requirement to improve outcomes in cardiac surgery. As Preoperative reduced left ventricular function has been recognized as the main risk factor for LCOS2.

Also peri-operative myocardial dysfunction is associated with organ failure, prolonged intensive-care stay, delayed recovery and prolonged hospital admissions3.

Postoperative acute kidney injury can be part of cardiorenal syndrome, which is a classic example of organ dysfunction that can arise due to hypoperfusion, which triggers a sympathoadrenergic response, hyperglycaemia and inflammation4.

Phosphodiesterase inhibitors, like milrinone, do the same by inhibiting cAMP degradation, this results in increased cellular energy demands and oxygen consumption, can trigger arrhythmias and can even be cardiotoxic5.

Inotropic support is frequently initiated in the perioperative period to improve post-bypass ventricular function. However, inotropes include the potential risk of increased myocardial oxygen consumption, which can result in cardiac ischaemia, with subsequent damage to hibernating but viable myocardium, and arrhythmias.

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This has prompted an ongoing debate on the potential harm associated with inotropic therapy in cardiac surgery. Indeed, the use of perioperative and postoperative inotropes has recently been found to be associated with increased mortality and major postoperative morbidity\(^6\).

In recent years, levosimendan is considered to be the ideal inotropic agent to support cardiac function in case of LCOS after cardiac surgery. Levosimendan is a calcium-sensitizing inotrope with a peripheral vasodilatory effect related to the ATP-sensitive potassium channel opening, and is able to increase cardiac output with minimal increase in myocardial oxygen consumption\(^6\).

The effects of levosimendan as an inodilator are based on a triple mechanism of action that provides positive inotropy with a neutral effect on oxygen consumption, and with preconditioning, cardioprotective, anti-stunning and anti-ischemic effects\(^7\).

In a recent meta-analysis of clinical trials, Mehta and colleagues evaluated the effects of levosimendan in cardiac surgery patients with and without preoperative systolic dysfunction\(^8\).

**Aim of the Work**

Our study is randomized, double-blind, placebo-controlled, multicenter clinical study to evaluate the efficacy of levosimendan given preoperatively in high-risk patients with LVEF ≤ 35\% undergoing cardiac surgery on CPB.

**II. Patients and Methods**

**Study objectives**

The primary objectives are to assess the effect of levosimendan on the incidence of renal replacement therapy through day 30 or post-operative MI or needing of mechanical assist device (IABP, extracorporeal membrane oxygenator) through day 5, and the incidence of death through postoperative day 60.

Secondary objectives are postoperative length of intensive care unit (ICU) stay, in hospital compiliation, out of hospital compiliation through day 30 and incidence of LCOS and effect on cardiac function, and postoperative use of inotropes through day 5.

**Study sites and patient population.**

This study was carried out in (Cardiothoracic Department Natinaol Heart Institute, Al Hussin hospital, Air Force Specialized hospital, Saudi Jerman hospital). Approximately 60 patients treated with study drug will be enrolled, the study population is drawn from patients with an LVEF ≤ 35\% scheduled to undergo cardiac surgery with planned CPB.

**Randomization and study drug administration**

Approximately 60 qualified patients will be randomly assigned, in a simple randomization scheme without stratification in a 1:1 ratio to receive either levosimendan or a blinded matching placebo.

Levosimendan (or placebo) infusion will be started after insertion of an arterial line and before skin incision at a dose of 0.2 μg kg\(^{-1}\) min for the first hour and then reduced to 0.1 μg kg\(^{-1}\) min to be continued for another 23 hours (total infusion time of 24 hours).

**Main criteria for inclusion and exclusion:**

Male and female patients who meet the following criteria will be enrolled:

**Main inclusion criteria:**

- Age ≥ 18 y
- Scheduled CABG, CABG with aortic valve, CABG with mitral valve or isolated mitral valve surgery with or without other valves
- Surgery will use CPB pump
- LVEF ≤ 35\% measured by echocardiogram, nuclear scan, or magnetic resonance imaging measured at any time within 30 d before surgery

**Main exclusion criteria:**

- Restrictive or obstructive cardiomyopathy, constrictive pericarditis, restrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output is dependent on venous return
- Evidence of systemic bacterial, systemic fungal, or viral infection within 72 h before surgery
- Chronic dialysis at the time of randomization (continuous venovenous hemofiltration, hemodialysis, ultrafiltration, or peritoneal dialysis within 30 d of CABG/mitral valve surgery)
- Estimated glomerular filtration rate 30 mL/min per 1.73 m\(^2\) before CABG/valve surgery
- Weight ≥ 150 kg
• Patients whose systolic blood pressure (SBP) cannot be managed to ensure SBP 90 mmHg at initiation of study drug
• Heart rate ≥120 beats/min, persistent for at least 10 min at screening and unresponsive to treatment
• Hemoglobin 8g/dL within 4 h before baseline
• Serum potassium 3.5 or 5.5 mmol/L at baseline
• Mechanical assist device (IABP, extracorporeal membrane oxygenation [ECMO]) placed at the start of surgery or preplanned to be placed during CABG/valve surgery before coming off the pump
• Patients with sartal femoral occlusive disease that would prohibit use of IABP and VAD and ECMO not available
• Liver dysfunction with Child Pugh class B or C
• Patients having severely compromised immune function
• Pregnant, suspected to be pregnant, or breast-feeding
• Known allergic reaction or sensitivity to levosimendan or excipients
• A history of torsade de pointes
• Received commercial levosimendan within 30 d before the planned start of study drug
• Received an experimental drug or used an experimental medical device within 30 d before the planned start of study drug

Data collection:
Patient information including demographics, medical history, physical examination, electrocardiogram (ECG) results, laboratory results, surgical procedural details,

Clinical follow up:
Patients were followed up clinically through postoperative day 30 and called at day 60 for ascertainment of vital status.

1) Post operative myocardial infarction
Blood samples for creatine kinase (CK), CK-MB will be collected and sent to the local laboratory at screening, within 8 hours before surgery, and at, 24, and 48 hours, and day 3,4 and day 5 after surgery.
Additional samples were drawn if clinically indicated for ischemic symptoms or for new-onset atrial fibrillation and ventricular arrhythmias.
An ECG will be recorded after surgery on days 0, 1, 2, 3, and 5, and on the day of and the day after the event for any new ischemic event through day 30.
MIs (through day 5) were defined as CK-MB 100 ng/mL (or CK-MB 10× upper limit of normal) irrespective of ECG changes, or CK-MB 50 ng/dL (or CK-MB 5× upper limit of normal) with evidence of new Q waves 30 ms in 2 contiguous leads, or new left bundle-branch block.

2) Post operative renal impairment and replacement therapy:
Renal replacement therapy included hemodialysis or other forms of dialytic support including peritoneal dialysis, or continuous venovenous hemodialysis.

3) Using of Mechanical assist devices:
Mechanical assist device use includes use of an IABP, extracorporeal membrane oxygenator.

4) Low cardiac output syndrome:
Low cardiac output syndrome is defined as cardiac index 2.4 L min/m2 for 30 minutes despite optimal fluid balance and maximal inotropic support (dobutamine, milrinone, epinephrine, norepinephrine), with the fluid balance and maximal inotropic dose at the investigator’s discretion. Postoperative use of secondary inotrope or vasopressors includes dobutamine, milrinone, epinephrine, or norepinephrine associated with index surgical procedure.

5) ICU length of stay.
6) Secondary inotropic use more than 24 h.
7) 30 days safety outcome.
On day 30 (+5 days), patients will be contacted by phone to collect information about survival status, postoperative MI (days 6-30), or postoperative dialysis beyond discharge up to 30 days.
In addition, information regarding rehospitalization at 30 days along with days and cause of rehospitalization will also be obtained.

8) 60 day survival state.
On day 60 (+5 days), patients will be contacted by phone to determine survival status.
Statistical Methods

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY). Continuous numerical variables were presented as mean and SD and inter-group differences were compared using the unpaired t-test. Categorical variables were presented as number and percentage and differences were compared using Fisher’s exact test. Ordinal data were compared using the chi-squared test for trend. Two-sided p-values <0.05 were considered statistically significant.

III. Results

Table (1): Demographic characteristics of both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan (n=30)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>15/15</td>
<td>14/16</td>
<td>1.0#</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.9 ± 14.6</td>
<td>49.3 ± 12.4</td>
<td>0.648</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.6 ± 4.9</td>
<td>34.9 ± 12.0</td>
<td>0.168</td>
</tr>
</tbody>
</table>

Data are ratio or mean ± SD.

*Unpaired t-test unless indicated.

#Fisher’s exact test.

This table shows no significant difference between Demographic characteristics among the studied groups. Levosimendan group includes 15 male and 15 female control Group includes 14 male and 16 female (30%), the mean age group of levosimendan group was (50.9 ± 14.6) while the mean age group of the control group was (49.3 ± 12.4).

Table (2): Average hemodynamic variables during 1st 24 hours after surgery in both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan (n=30)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>97.0 ± 16.3</td>
<td>102.0 ± 11.0</td>
<td>0.173</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>74.4 ± 16.3</td>
<td>63.7 ± 13.0</td>
<td>0.006</td>
</tr>
<tr>
<td>CVP (cmH₂O)</td>
<td>12.8 ± 3.8</td>
<td>13.1 ± 2.3</td>
<td>0.744</td>
</tr>
<tr>
<td>Serum lactate (mmol/l)</td>
<td>4.3 ± 3.9</td>
<td>8.8 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>59.8 ± 8.7</td>
<td>50.4 ± 7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO₂ gap (mmHg)</td>
<td>5.2 ± 2.3</td>
<td>2.7 ± 0.8</td>
<td>0.032</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>64.7 ± 12.1</td>
<td>55.7 ± 12.1</td>
<td>0.05</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>5.2 ± 1.4</td>
<td>4.5 ± 0.8</td>
<td>0.009</td>
</tr>
<tr>
<td>EF (%)</td>
<td>35.1 ± 8.8</td>
<td>26 ± 9.1</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation (SD).

*Unpaired t-test.

There was a statistical significant difference between the studied groups in serum lactate level, venous saturation, CO2 gap, stroke volume, cardiac output, mean arterial blood pressure and left ventricular function in the first 24 hr after surgery. The serum lactate at the after 24 hr in the levosimendan group was lower than control group (4.3±3.9) in levosimendan group and (8.8±3.0) in control group (p value <0.001).

Central venous saturation was higher in levosimendan group (59.8±8.7) than in control group (50.4±2.7) (p value = 0.032), CO2 gap in the levsindan group was (5.2±1.4) lower than control group (5.6±2.7)(p value =0.032). The stroke volume and cardiac output in the levosimendan group are higher than the control group, levosimendan group SV and CO was (64.7±12.1),(5.2±1.4) However in the control group (55.7±12.1)(4.5±0.8).

Left ventricular function improved in the levosimendan group (35.1±8.8). Than the control group (26±9.1)(p value =0.044).

Table (3): Urine output in 1st 5 days after surgery in both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan (n=30)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOP (ml/24 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1695.0 ± 577.5</td>
<td>1513.3 ± 282.5</td>
<td>0.129</td>
</tr>
<tr>
<td>Day 2</td>
<td>2413.3 ± 856.5</td>
<td>2086.7 ± 590.0</td>
<td>0.091</td>
</tr>
<tr>
<td>Day 3</td>
<td>2526.7 ± 1029.4</td>
<td>2161.7 ± 881.3</td>
<td>0.146</td>
</tr>
<tr>
<td>Day 4</td>
<td>2651.7 ± 1205.9</td>
<td>2276.7 ± 1150.8</td>
<td>0.223</td>
</tr>
<tr>
<td>Day 5</td>
<td>2465.0 ± 1305.4</td>
<td>2126.7 ± 1280.3</td>
<td>0.315</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation (SD).
*Unpaired t-test.
This table shows no significant difference regarding **Urine output in 1st 5 days after surgery in both study groups**

Table (4): Serum creatinine in 1st 5 days after surgery in both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan (n=30)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1.6</td>
<td>1.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Day 2</td>
<td>1.6</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Day 3</td>
<td>1.9</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Day 4</td>
<td>2.0</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Day 5</td>
<td>1.9</td>
<td>2.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation (SD).

*Unpaired t-test.
This table shows no significant difference regarding **Serum creatinine in 1st 5 days after surgery in both study groups**

Table (5): Cardiac index in 1st 5 days after surgery in both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan (n=30)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>2.6</td>
<td>2.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Day 2</td>
<td>2.7</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Day 3</td>
<td>2.8</td>
<td>2.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Day 4</td>
<td>2.9</td>
<td>2.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Day 5</td>
<td>3.0</td>
<td>2.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation (SD).

*Unpaired t-test.
This table shows significant difference in the cardiac index in the first day after surgery p value =0.017

Table (6): Serum lactate in 1st 5 days after surgery in both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan (n=30)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum lactate (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>6.5</td>
<td>8.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Day 2</td>
<td>4.3</td>
<td>6.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Day 3</td>
<td>3.6</td>
<td>4.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Day 4</td>
<td>3.1</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Day 5</td>
<td>3.0</td>
<td>3.9</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation (SD).

*Unpaired t-test.
This table shows significant difference in the serum lactate in the first and second day after surgery p value =0.008 and 0.018 respectively

Table (7): Cardiac enzymes in 1st 5 days after surgery in both study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan (n=30)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK (IU/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3094.5</td>
<td>2300.8</td>
<td>4848.4</td>
</tr>
<tr>
<td>Day 2</td>
<td>2450.0</td>
<td>2338.6</td>
<td>4491.3</td>
</tr>
<tr>
<td>Day 3</td>
<td>2035.4</td>
<td>2545.2</td>
<td>3310.6</td>
</tr>
<tr>
<td>Day 4</td>
<td>1303.1</td>
<td>1896.2</td>
<td>2560.2</td>
</tr>
<tr>
<td>Day 5</td>
<td>1136.1</td>
<td>2196.3</td>
<td>1553.9</td>
</tr>
<tr>
<td>CKMB (IU/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>163.0</td>
<td>137.4</td>
<td>265.3</td>
</tr>
<tr>
<td>Day 2</td>
<td>203.8</td>
<td>416.6</td>
<td>188.1</td>
</tr>
<tr>
<td>Day 3</td>
<td>94.2</td>
<td>138.7</td>
<td>166.8</td>
</tr>
<tr>
<td>Day 4</td>
<td>58.0</td>
<td>100.3</td>
<td>123.8</td>
</tr>
<tr>
<td>Day 5</td>
<td>48.4</td>
<td>114.5</td>
<td>90.2</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation (SD).

*Unpaired t-test.
This table shows significant difference in the Cardiac enzymes*( CK (IU/l) in the first and second day after surgery p value =0.008 and 0.007 and significant difference CKMB (IU/l) in the day 1 and day 4 p value =0.006and 0.021

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In our study the baseline demographic data were almost equal in both study groups with no significant difference regarding preoperative comorbidities, preoperative medication, hemodynamics variables.

Regarding preoperative comorbidity and past medical history it was concordant with other international studies like De Hert et al., who conducted a study enrolling 30 patients evaluating the Effects of Levosimendan in Cardiac Surgery Patients with Poor Left Ventricular Function had found that there was no difference in Body mass Index among levosimendan group mean±SD 26.3±3.6 and conventional group (milrinone) mean±SD 26.2±3.7. According to pre operative comorbidity and past medical history our study also showed no significant statistical difference regarding preoperative comorbidities, preoperative medication, hemodynamics, labs, Echo finding, as well as the NYHA class of both study groups which showed almost the similar characteristics of both study groups.

Those co morbid factors are important risk factors for cardiac disease, there was same concern from other international studies about those co morbid factors.

Our study did not seek for certain type of cardiac surgery to be included in the study with variations of types of surgical procedures but as usual the most of the included cases was CABG or valve replacement surgery, with extension of spectrum of surgical procures to different types like bental and other surgeries but without domination of one type over others.

But this is discordant with Alvarez et al., who conducted a study enrolling 50 patient evaluating the Hemodynamic Effects of Levosimendan Compared With Dobutamine in Patients With Low Cardiac Output After Cardiac Surgery had found that 12(57%) patients had CABG operation among levosimendan group while 9(45%) patients had CABG among conventional (dobutamine) group.

Additionally, De Hert et al., stated that 5 patients done CABG among levosimendan group, 4 patients done CABG for conventional (milrinone) group.
It also disconcordant, Klasnja et al. (10), who conducted a study enrolling 12 patients evaluating the Hemodynamic Effects of Levosimendan for Low Cardiac Output After Cardiac Surgery) determined that upper hand for CABG operation 8 patients while valve operation were 4 patients.

We think that is due to low percentage of valve surgery in other country due to deficiency of main valve pathology which leading to valve surgery which is rheumatic heart disease however it is more prominent in Egypt.

Aortic cross-clamping and CPB time in both study groups:

In our study, the use of levosimendan pre and early postoperative was associated with facilitate weaning from bypass machinethe mean±SD of cross calming time and total bypass time of levosimendan group was significantly shorter (65.5±51.0) (p=0.03) in comparison with control group (98.0±55.0) while mean±SD of cross calming time and total bypass time respectively of control group was (111.5±44.0), (148±60.3) and p value, (p=0.02).

Additionally, in the randomized, double-blind Eriksson et al. (11), in the LEWE study (levosimendan facilitate weaning from cardiopulmonary bypass), levosimendan facilitated weaning from CPB and reduced the need for additional inotropic or mechanical circulatory support in patients with impaired LVEF (<50%) undergoing CABG. 60 patients received either Levosimendan as a 12 mic/kg bolus followed by 0.2 mic/kg/min infusion, or placebo, started immediately after the induction of anesthesia had found that Levosimendan significantly facilitated primary weaning from CPB as compared with placebo (P=0.002). Four patients in the placebo group even failed the second weaning and had to be supported by IABP, as compared with none in the levosimendan group (P=0.112).

Disconcordant to our result Gandhamet al. (12), who conducted a study enrolling 60 patients evaluating a comparison of hemodynamic effects of levosimendan and dobutamine in patients undergoing mitral valve repair / replacement for severe mitral stenosis found that duration of bypass machine was less with conventional group than levosimendan group 88.7±10.63 (min) VS 92.9±9.95 (min) this discrepancy between their result and our result may be explained by the lower age group recruited to undergo cardiac surgery for mitral valve replacement.

Hemodynamic variables at end of surgery in both study groups

In our study the heart rate showed no significant statistical difference at all times postoperative between both groups p>0.05. This went side by side with De Hert et al. (8) who states that there was no statistically difference in the heart rate at all times postoperative between both groups (p>0.05).

Also, Malliotakis et al. (9) stated that there was no significant changes in heart rate postoperative (p>0.05).

In contrast, Gandhamet al. (12) showed there was significance difference in heart rate being higher in the conventional group mostly all times postoperative p<0.05 this variance may be due to that he was mainly comparing dobutamine with levosimendan.

In our recent study the mean arterial pressure was statistically significant at 24 hrs postoperative p value = 0.006 respectively being higher in the levosimendan group than in control group.

This was concordance, Alvarez et al. (9) showing that there was significance mean arterial pressure difference between both groups 6, 12, 24, 48hrs postoperative p <0.05 being higher in the conventional group.

In our study evaluating central venous pressure immediately post operative and 24 hrs postoperative were statistically not significant between both groups being lower in the levosimendan group.

Our results disconcordance to other studies like, Alvarez et al. (9) had found that significant difference in central venous pressure at 6, 12, 24, 48hrs postoperative between both groups with p<0.05.

Malliotakis et al. (10) determined that there was significant difference in central venous pressure at 6, 12, 24hrs postoperative from baseline levosimendan infusion p<0.05.

Gandhamet al. (12) found that there was significant difference in central venous pressure at immediate, 6,12hrs postoperative from baseline levosimendan infusion with p<0.05.

They all found that there were significant reduction in central venous pressure in levosimendan group as a result of reduction in systemic and pulmonary vascular resistance this variation matched without study.

In the current work we used CO2 gap, mixed venous saturation and serum lactate being an indicator for adequate cardiac output and tissue perfusion they were highly significant at almost all times postoperative p <0.05.

In concordance with other studies Alvarez et al. (9) showed that significant difference in mixed venous oxygen saturation at 6, 12, 24, 48hrs postoperative between both groups with p<0.05.

Malliotakis et al. (10) determined that there was significant difference in mixed venous oxygen saturation at 6, 12, 24hrs postoperative from baseline levosimendan infusion p<0.05.
In contrast to our results, the double blind, randomized trial by Shahet al.\cite{14}, tested preoperatively administered levosimendan 200mcg/kg infusion for 24h against placebo for off pump CABG in 50 patients with left ventricular dysfunction (LVEF <30%). As compared to the control group, thelevosimendan-treated patients had maintained hemodynamic with higher cardiac index and PCWP during the operative and early postoperative periods.

Also our result in In concordance with Mehta et al.\cite{13} (Levo CTS trial), the study population consisted of 882 patients with low preoperative LVEF (EF, 35%) undergoing scheduled or urgent cardiac surgery (CABG and/or mitral valve surgery with or without involvement of other valves).

All patients were considered at risk of developing postoperative LCOS. Levosimendan (0.2 mcg kg.minfor 60 minutes, followed by 0.1mcg.kg.min21 for 23 hours) or placebo was started at the induction of anesthesia to assess whether the drug would decrease the development of LCOS and its detrimental consequences. The study, conducted at 70 sites in Canada and the United States, demonstrated no statistically robust treatment effect on the composite primary end point of death, perioperative myocardial infarction, and need for renal replacement therapy or a mechanical ventilator assist device. However, there were fewer deaths in the levosimendan group: 20/428 (4.7%) versus 30/421 (7.1%), odds ratio 0.64, 95% CI, 0.37–1.13 (P = 0.12)\cite{13}.

In addition, the levosimendan-treated patients experienced statistically significantly fewer LCOS events (78 vs. 108; P = 0.007) and needed less inotropic support at or beyond 24 hours after initiation of infusion (235 vs. 264, P = 0.02). Cardiac index also improved more in levosimendan-treated patients (2.9 +0.6vs. 2.7 + 0.7 L/min P < 0.001).

In concordance with other studies Lomivorotovet al.\cite{18} Levosimendan was shown to be effective in reducing low cardiac output syndrome when compared with placebo [107 of 723 (14.8%) in the levosimendan group vs 207 of 715 (29.0%) in the placebo group] (RR = 0.40, 95% CI = 0.22–0.73; P = 0.003; 12 = 75%; for heterogeneity = 0.003, with 1438 patients included and 6 RCTs).

Additionally, Levinet al.\cite{146}, showed that the preoperative use of levosimendan started 24h before surgery, with a loading dose of 10micg/kg infusion for 1h that was followed by continuous infusion of 0.1micg/kg /min infusion for 23h Levosimendan result in well maintained hemodynamic and reduce the incidence of LCOS(low cardiac output syndrome) (7.1%vs.20.8%;P value= 0.05) and of complicated weaning from CPB (2.4%vs.9.6%;P value= 0.05).

Supporting our work, Toller et al.\cite{137}, had published an article in the journal of cardiothoracic and vascular anesthesia may 2012 titled Perioperative use of levosimendan best practice in operative setting had found that administering the drug in the ICU (late postoperative) in the event of LCOS (low cardiac output syndrome) result in unfavorable outcome However, early treatment reflects better results. Therefore, levosimendan should not be used as a last resort, and its administration should not be delayed after other drugs /techniques/ strategies have failed and organ failure already is present.

In our study, the early use of levosimendan had significantly increase postoperative ejection fraction than the postoperative ejection fraction with the preoperative, intra operative and/or postoperative use of levosimendan p<0.001

In concordance to our results, Ersoyet al.\cite{18} who conducted a retrospective study enrolling 40 patients within 4groups 10 patient each group/infusion of Levosimendan, applied 12h before operation(G1), after induction of anesthesia (G2), during the pump removal(G3)and non-levosimendan group(G4) evaluating the effect of Preoperative uses of levosimendan in patients undergoing coronary artery bypass grafting (CABG, LVEF <30%).(0.2 mic /kg/min infusion) result in Increase of LVEF and less myocardial damage in the group used levosimendan 12h before surgery.

Also, the double blind randomized trial by Shah et al.\cite{14}tested preoperatively administered levosimendan 200mic/kg infusion for 24h against placebo for off pump CABG in 50 patients with left ventricular dysfunction (LVEF <30%). As compared to the control group, thelevosimendan-treated patients had higher cardiac index and PCWP during the operative and early postoperative periods.

Hand by hand Lepikkangas et al.\cite{19} (stated Preoperative levosimendan infusion in combined aortic valve and coronary bypass surgery 12 mic bolus for 10 min followed by 0.2mic/kg/min infusion for 24h; treatment was started on the day before surgery result in Higher cardiac index and stroke volume index with levosimendan for the 4-day postoperative period(P < 0.05). LVEF maintained in the levosimendan group while the control group showed a decrease LVEF).

Similarly, Reynolds et al.\cite{20}, who conducted a Prospective randomized double-blind vs. placebo on 24 cardiac surgical patients evaluating the effect of Levosimendan in aortic valve surgery: cardiac performance and recovery. (12patients each group) patients received levosimendan 0.2mic/kg/min infusion for 24h beginning after the induction of anesthesia result in LVEF was maintained with levosimendan but dropped with placebo.

Additionally, Barisinet al.\cite{21}, who conducted a study on 24 cardiac surgery patients evaluating the effect of Levosimendan as a new strategy during off pump coronary artery bypass grafting: double blind,
randomized, placebo controlled trial had found that levosimendan at a dose of 12 mic/kg as an infusion for 15 min before CABG. At 10 min and 60 min post-infusion, the cardiac index and the LVEF were significantly higher with levosimendan than with placebo (P=0.018 each). The stroke volume index was significantly higher for levosimendan at 10 min (P=0.018), but not at 60 min (P=0.063).

In addition, S. Barisinet et al. (21), had found a significant increase in cardiac output and LVEF occurred after high-dose (P=0.001, P=0.006) and low dose levosimendan (P=0.001, P=0.002). Both levosimendan doses produced a significant increase in stroke volume and decreased systemic vascular resistance.

Sixty-day survival in both study group

In our study, mortality incidence with use of levosimendan was lower than mortality with control group in the preoperative, use of levosimendan 4 cases died during the 60 days follow up in levosimendan group while 7 cases died in the control group; the p value does not reach the significant value.

In discordance with our work, Levint et al. (16), had found that the preoperative use of levosimendan in high-risk patients with severe left ventricular dysfunction (LVEF <25%) scheduled for CABG was assessed in a randomized, placebo-controlled trial. Levosimendan was started 24 h before surgery, with a loading dose of 10 mic/kg infusion for 1 h that was followed by continuous infusion of 0.1 mic/kg/min infusion for 23 h. Overall, 252 patients participated in the study. Levosimendan reduced mortality compared to placebo (3.9%/vs. 12.8%; P value = 0.05).

In concordance with Landoni et al. (22) (CHEETAH Study Group), levosimendan for hemodynamic support after cardiac surgery, levosimendan or placebo was administered to cardiac surgery patients, who, according to predefined criteria, developed postoperative LCOS.

In total, 1000 patients were scheduled to be included and the primary end point was 30-day mortality. A total of 248 patients received levosimendan and 258 received placebo. There was no significant difference in 30-day mortality between the levosimendan and placebo groups: 32 patients (12.9%) versus 33 (12.8%); absolute risk difference 0.1 percentage Points.

This variation from our work could be explained by that they were working on a large number of study population 880 patients in Mehta et al. (19) study and 200 patients in Lahtinen et al. (23) study.

V. Conclusion

Despite recent therapeutic and technological advances in cardiac surgery, many patients with reduced LVEF undergoing cardiac surgery on CPB remain at high risk for perioperative adverse outcomes, including LCOS. Currently available options to prevent and/or treat complications after cardiac surgery, particularly LCOS, lack robust data supporting their efficacy, are not widely available, and can be prohibitively expensive.

Data from our study will provide insight into the efficacy, safety, of levosimendan in reducing short-term morbidity and mortality in high-risk patients undergoing cardiac surgery on CPB.

VI. Recommendations

Our study, recommended that a prophylactic infusion of levosimendan started immediately before surgery reduces LCOS in a heterogeneous population of cardiac surgery patients with reduced LVEF with fewer deaths in the levosimendan group and needed less inotropic support at or beyond 24 hours after initiation of infusion.

References


DOI: 10.9790/0853-1809130110 www.iosrjournals.org 9 | Page
Perioperative Use of Levosimendan in Patients with Left Ventricular Systolic Dysfunction


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