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The Role of Levosimendan as Inotropic Agents in Patients with LV Dysfunction Admitted to ICU Post Cardiac Surgery

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***Abstract*---**Coronary artery bypass graft (CABG) surgery is the standard of care for the management of patients with three-vessel and left main coronary artery disease (CAD) with viable myocardium. Positive inotropic agents are the treatment of choice in patients with LV dysfunction post CABG. Levosimendan is an inotropic drug that has three major mechanisms of action: positive inotropy, vasodilation, and cardiac cytoprotection. Levosimendan is a calcium sensitizer, it improves myocardial contractility by sensitising troponin C to calcium without increasing myocardial oxygen consumption and without impairing relaxation and diastolic function. The aim of this study was to determine the effect of levosimendan compared to the conventional inotropic agents on the outcomes of patients with LV dysfunction undergoing CABG. It is a prospective observational study that patients were divided into 2 groups of 50 patients each. Group A received intravenous levosimendan (at a dose of 0.2µg per kilogram of body weight per minute for 1 hour, followed by a dose of 0.1µg per kilogram per minute for 23 hours), with the infusion started at the induction of anesthesia while Group B which included patients who received conventional drugs. Clinical examination, Hemodynamic data and

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Laboratory investigations pre-operative and post-operative were collected. Our study showed that Levosimendan had significantly improved postoperative outcomes. There was statistically significant difference between studied groups in terms of postoperative LVEF (p =0.075). Also, there was statistically significant difference between studied groups in terms of ICU stay (0.002). Moreover, There was statistically significant difference between studied groups in terms of mortality (p =0.004). Levosimendan administration was associated with reduced mortality in patients and shorter ICU stays with LV dysfunction post CABG. Furthermore, levosimendan can help reduce the incidence of LCOS and thereby reduce the complications associated with LCOS.

***Keywords*---**levosimendan, LV dysfunction, cardiac surgery, inotropic support, low cardiac output.

Introduction

Coronary artery bypass graft (CABG) surgery is the standard of care for the management of patients with three-vessel and left main coronary artery disease (CAD) with viable myocardium, The optimal strategy for management of patients with CAD and severe left ventricular (LV) dysfunction [ejection fraction (EF) ≤ 40%] is not clear, However several studies have demonstrated reduced operative mortality and improved short and long-term survival benefits following CABG among patients with severe LV dysfunction (1). Pharmacological support, in the form of Catecholamines is the first line of LCOS therapy, to be initiated as soon as the volume status is optimized, the use of inotropes and vasodilators to improve contractility, preload, and afterload. Nevertheless, inotropic agents, which are used primarily in patients with LCOS, also can improve CO, but they achieve this goal at the expense of increased myocardial consumption and an increased mortality risk (2)

Levosimendan is a calcium sensitizer that increases cardiac contractility without increasing intracellular calcium or oxygen consumption and induces vasodilation (3). Levosimendan is characterised by a triple mechanism of action; i.e., it acts via calcium-dependent binding to cardiac troponin C, and opens the KATP channels on smooth muscle cells in the vasculature, and in cardiac mitochondria. This binding of levosimendan to troponin C and the opening of K_{ATP} channels on smooth muscle cells in the vessels result in its inotropic and vasodilatory effects, respectively, while the opening of K_{ATP} channels in cardiac mitochondria is believed to be a cardioprotective pathway (4). Levosimendan reduces peripheral vascular resistance and has direct contractility-enhancing effects on the failing left ventricle. It also improves indices of diastolic function and seems to improve the function of stunned myocardium. Despite an improvement in ventricular function, levosimendan does not increase myocardial oxygen uptake significantly. An increase in coronary blood flow and a reduction in coronary vascular resistance have been observed (5). Common adverse effects reported are hypotension, headache, and dizziness secondary to the vasodilating properties.

Increased incidence of atrial fibrillation has also been associated with infusion of levosimendan compared with both dobutamine and conventional drugs (6).

Patients and Methods

The present study was a prospective observational study that carried out from March 2018 to march 2020 in which patients admitted to the intensive care units following CABG with LV dysfunction in Agouza Police hospital. A total of 100 patients were enrolled in our study and were subsequently divided into two groups 50 patients each, Group (A) received intravenous levosimendan (at a dose of 0.2 μg per kilogram of body weight per minute for 1 hour, followed by a dose of 0.1 μg per kilogram per minute for 23 hours), with the infusion started at induction of anesthesia while Group (B) received conventional drugs (inotropic and vasopressor treatment).

Inclusion and Exclusion Criteria

We included patients who fulfilled the following criteria: Patients undergoing isolated on-pump CABG (Patients with LV dysfunction with EF ≤ 35%), Age group between 18 and 70 years old. We excluded the following criteria: Patients with normal LV functions undergoing CABG, patients diagnosed preoperatively with AF or have history of AF, patients with end stage renal disease (ESRD) on hemodialysis and patients who refuse to participate in the study. Study's Procedure and Data Collection: The following data were collected from every eligible participant: Full history taking and clinical examination. Echocardiography pre-operative and post-operative after 48hours (EF was measured by M-mode). Laboratory pre-operative and post-operative including: Complete blood count, renal and liver function tests, coagulation profile and cardiac enzymes, data collection to evaluate incidence of complications postoperative in the ICU, ECG and incidence of perioperative cardiac events (MI and arrhythmia).

Statistical analysis

Data were collected, revised, coded and entered to the statistical package for social science. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SPSS Inc, and Chicago, IL, USA). The normality of the data were assessed using Shapiro-Wilk Test. Numerical data were described as mean ±SD if normally distributed; or median and interquartile range [IQR] if not normally distributed. Frequency tables with percentages were used for categorical variables. Independent Student t-test and paired t-test were used to compare parametric quantitative variables; while Mann-Whitney tests and Wilcoxon matched pairs test were used to compare non-parametric quantitative variables. Chi-square test was used to analyze categorical variables. Multilinear logistic regression was undertaken to assess the predictors of study's outcomes. A p-value < 0.05 is considered statistically significant.

Results

Our study enrolled a total of 100 patients who were admitted to ICU following cardiac surgery with preoperative echocardiography revealing impaired cardiac functions EF < 35%. The demographic characteristics of the included patients in levosimendan group their mean age was 61.72±9.9 in comparison to their median range was 65 and the majority of patients were males with percentage 78%. The hypertensive patients with percentage 66%, the diabetic patients were 22% while 12% of the patients were hypertensive and diabetics. Table (1)

In our study the postoperative outcome in group A showed that myocardial infarction occurred in 16% of the patients, Use of IABP occurred in 30% of the patients , 48% of the patients developed arrhythmia mostly AF. Moreover, reversible renal impairment occurred in12% of the patients, ESRD with regular hemodialysis occurred in 2% of the patients, cerebrovascular stroke occurred in 2% of the patients, VF occurred in 2% of the patients, Transient liver impairment occurred in 26% of the patients, NSTEMI occurred in 12% of the patients, ICU Psychosis occurred in 6% of the patients. The mean length of stay in the ICU was 3.92 ±1.8 with median range 4 while death of 18% of the patients occurred. Table (2), Figure (1)

Our study shows that there were no statistically significant differences between studied groups in terms of preoperative LVEF (p =0.445). Table (3). Our study shows that there was statistically significant difference between studied groups in terms of postoperative LVEF (p =0.075). Table (4), Figure (2). Our study shows that there were no statistically significant differences between studied groups in terms of myocardial infarction (p =0.72), and use of mechanical cardiac assist device (IABP) (p =0.107). Furthermore, there were no statistically significant differences in terms of postoperative arrhythmia mostly AF (p =0.68), and incidence of postoperative events (Reversible Renal impairment, ESRD, Stroke, VF, Transient liver impairment, NSTEMI, Psychosis) (p =0.25). On the contrary, there was statistically significant difference between studied groups in terms of ICU stay (p =0.002). Patients in levosimendan group had significantly shorter ICU stay. Also, there was statistically significant difference in terms of mortality (p =0.004). Patients in levosimendan group had significantly lower mortality rate. Table (5), Figure (3)

Table 1
The demographic characteristics of the included patients in levosimendan group

Variables	Patients (N =50)
Age in years	
- Mean ±SD	61.72 ±9.9
- Median (Range)	65 (33 -78)
BMI in Kg/m^2	
- Mean ±SD	28.8 ±4.2
- Median (Range)	28.5 (20 - 38)
Gender, No (%)	

- Male	39 (78%)
- Female	11 (22%)
Comorbidities, No (%)	
- DM	11 (22%)
- HTN	33 (66%)
- HTN and DM	6 (12%)

Table 2
Outcomes of the included patients in levosimendan group

Variables	Patients (N =50)
Myocardial infarction, No (%)	
- Yes	8 (16%)
- No	42 (84%)
Use of mechanical cardiac assist device (IABP), No (%)	
- Yes	15 (30%)
- No	35 (70%)
Postoperative Arrythmia mostly AF, No (%)	
- Yes	24 (48%)
- No	26 (52%)
Postoperative events, No (%)	
- Yes	31 (62%)
- No	19 (38%)
Type of complications, No (%)	
- Reversible Renal impairment	6 (12%)
- ESRD	1 (2%)
- Stroke	1 (2%)
- VF	1 (2%)
- Transient liver impairment	13 (26%)
- NSTEMI	6 (12%)
- Psychosis	3 (6%)
ICU Stay in days	
- Mean ±SD	3.92 ±1.8
- Median (Range)	4 (1 -10)
Death , No (%)	
- Yes	9 (18%)
- No	41 (82%)

*Data are presented as mean ±SD, median (Range), or number (%).

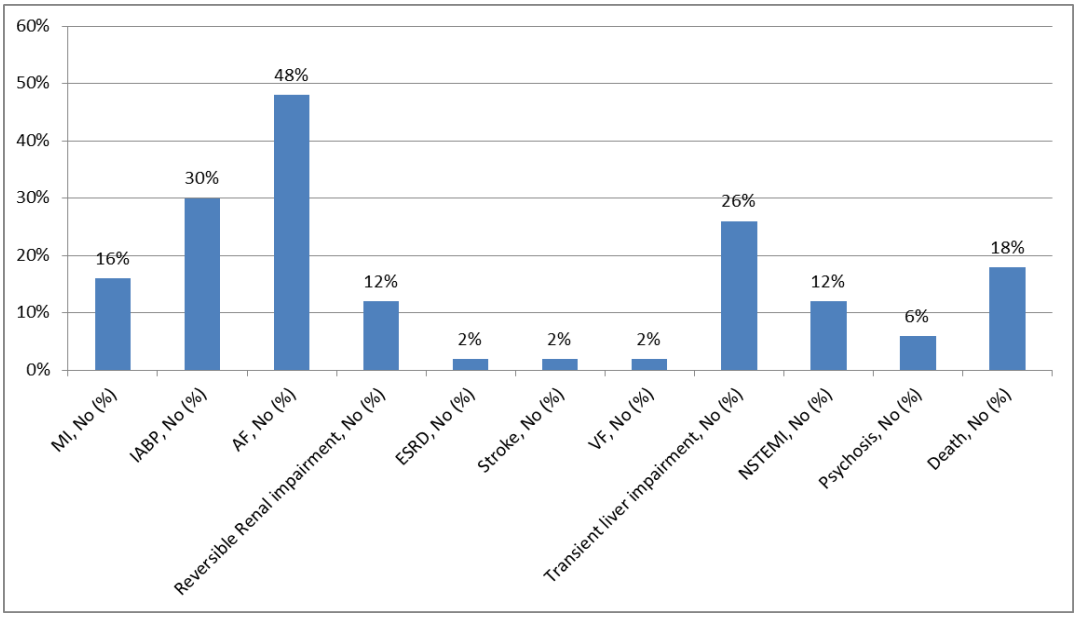

Figure 1. Distribution of outcomes

Table 3
The difference in preoperative cardiac function among studied groups

Variables	Group A (N =50)	Group B (N =50)	P-value
LVEF in % - Mean ±SD - Median (Range)	 29.54 ±9.9 30 (18 -35)	 30.1 ±3.2 30 (26 -35)	 0.445

*Data are presented as mean ±SD, median (Range), or number (%).

Table 4
The difference in postoperative cardiac function of the studied groups

Variables	Group A (N =50)	Group B (N =50)	P-value
LVEF in % - Mean ±SD - Median (Range)	 33.32 ±7.4 33 (20 -45)	 30.82 ±6.4 30 (20 -45)	 0.075

*Data are presented as mean ±SD, median (Range), or number (%).

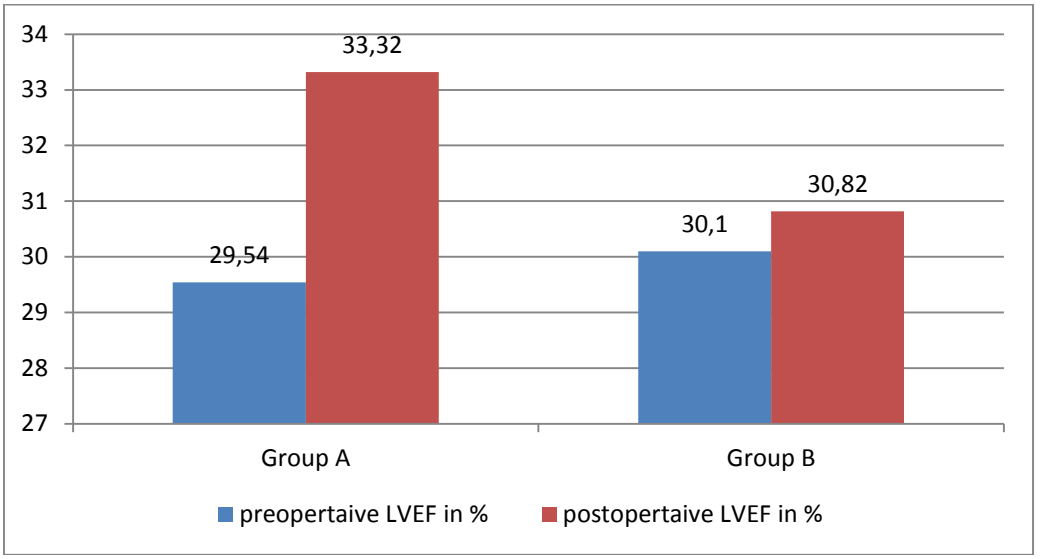

Figure 2. The difference in preoperative and postoperative LVEF among studied groups

Table 5
The difference in outcomes among studied groups

Variables	Group A (N =50)	Group B (N =50)	RR, 95% CI*	P-value
Myocardial infarction, No (%) - Yes - No	 8 (16%) 42 (84%)	 7 (14%) 43 (86%)	 1.14 (0.45 - 2.91)	 0.72
Use of mechanical cardiac assist device (IABP), No (%) - Yes - No	 15 (30%) 35 (70%)	 22 (44%) 28 (56%)	 0.68 (0.41 - 1.15)	 0.107
Postoperative Arrythmia, mostly AF, No (%) - Yes - No	24 (48%) 26 (52%)	22 (44%) 28 (56%)	1.1 (0.71 - 1.66)	0.68
Postoperative events, No (%) - Yes - No	 31 (62%) 19 (38%)	 36 (72%) 14 (28%)	 0.86 (0.65 - 1.13)	 0.25
ICU Stay in days - Mean ±SD - Median (Range)	 3.92 ±1.8 4 (1 -10)	 4.92 ±1.5 4 (3 -7)	 -----	 0.002
Death, No (%) - Yes	 9 (18%)	 22 (44%)	 0.41	 0.004

- No	41 (82%)	28 (56%)	(0.21 - 0.79)	

*Data are presented as mean ±SD, median (Range), or number (%)

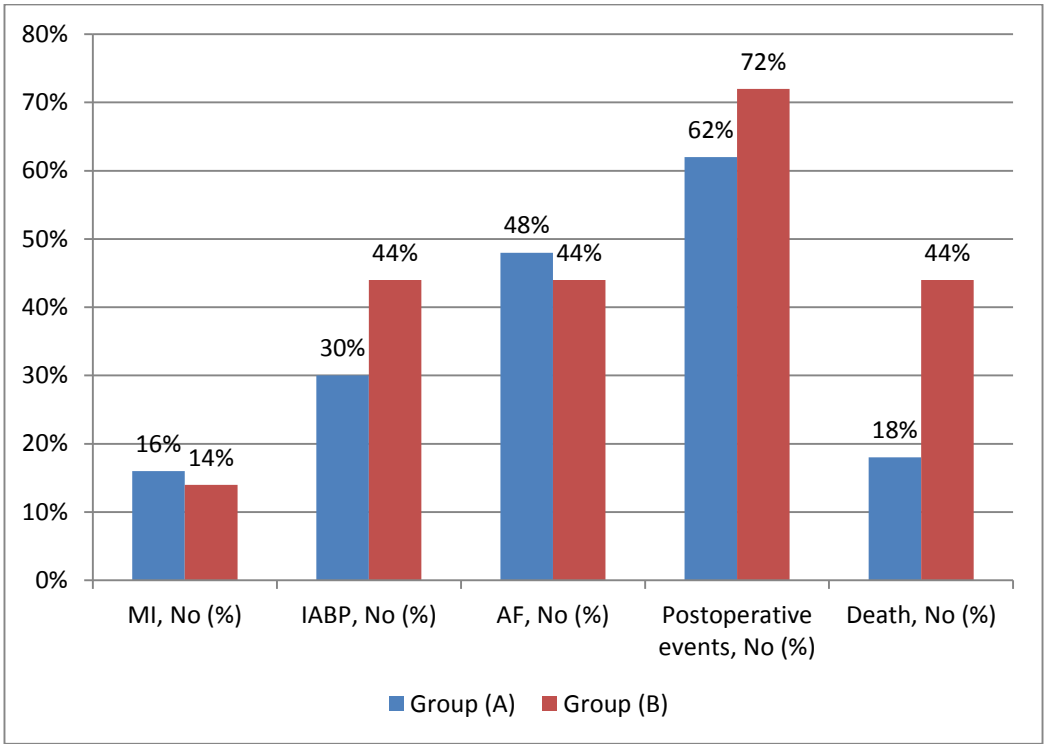

Figure 3. The difference in outcomes among studied groups

Discussion

The low cardiac output syndrome is a postoperative complication defined as the need for catecholamine infusion or mechanical assist device to maintain adequate arterial blood pressure and cardiac index. Patients with low cardiac output syndrome also have a high rate of renal failure (≈ 20%) as a consequence of inadequate tissue perfusion. Therefore, if a patient does not require prolonged postoperative catecholamine infusion, mechanical assist device, or renal replacement therapy, it is unlikely that he or she has experienced low cardiac output syndrome. This is why the combination of these 3 clinical markers was chosen as a simple and robust primary end point to evaluate the efficacy of levosimendan (7).

In our study using of levosimendan achieved statistically significant improvement in left ventricular function (EF%) postoperatively determined by echocardiography compared to conventional group (33.32 ±7.4 VS 30.82 ±6.4)(P value 0.075)
Supporting our study Huang et al levosimendan use was significantly associated with a lower level of blood lactate and higher cardiac index, fluid requirement, significant increases in cardiac output and left ventricular ejection fraction occurred, when compared with control group which lead to significant reduction in mortality rate among the patients (8)

In concordance to our study, Barisin S et al., (9) in his study levosimendan in off-pump coronary artery bypass: a Four-time masked, controlled study enrolling 31 patients: 10 patients received a high dose, 10 patients received a low dose, and 11 patients received a placebo. Regarding our study showed that renal impairment occurred in 12% of the patients of group (A) which is equal to group (B) with no statistically significant differences between studied groups. These findings were similar to the result found by Jawitz, et al. who demonstrate no significant association between levosimendan infusion and the occurrence of postoperative AKI. (10).

The outcome of our study revealed ESRD with regular hemodialysis occurred in 2% of the patients, however, Lannemyr, et al. reported that levosimendan increases glomerular filtration rate and thus may be the preferred inotropic agent for treating patients with the cardiorenal syndrome (11) which is comparable with Guerrero-Orriach, et al. who found that levels of creatinine decreased in the levosimendan treated patients, showing significant variations at 24 and 48 h after treatment (12). Our study showed that there were no statistically significant differences between studied groups in myocardial infarction. These results were similar to Zhu, et al. (13). Moreover, Wang, et al, 2019 proclaimed that levosimendan significantly reduced the incidence of postoperative MI (14). Although vasodilation caused by levosimendan is regarded as a side effect, which might lead to hypotension, it does provide organ protection against ischemia which has been suggested by Zangrillo, et al. (15).

There was statistically significant difference between studied groups in terms of ICU stay ($p = 0.002$) in our study. Patients in levosimendan group had significantly shorter ICU stay which is compatible with Maharaj, et al. who declared that the use of levosimendan is associated with improvement in haemodynamics and reduction in cardiac biomarkers which lead to shorting in the length of ICU stay (16). Several studies found that levosimendan produces sustained increases in cardiac output and heart rate, and reductions in mean arterial pressure, systemic vascular resistance and pulmonary capillary wedge pressure in patients with normal ventricular function (17). Our study has generally reported results potentially suggestive of a decreased incidence of mortality in levosimendan group which is noted by Maharaj, et al., 2011 that the use of levosimendan in patients having coronary revascularization is associated with a significant reduction in mortality (16). Also, Zangrillo, et al. recorded in their analysis that levosimendan might reduce mortality in a patients with severe sepsis and septic shock when compared with conventional inotropic therapy (18). Interestingly, other studies showed that levosimendan use was significantly associated with a lower level of blood lactate and higher cardiac index, fluid requirement, significant increases in cardiac output and left ventricular ejection fraction occurred, when compared with control group which lead to significant reduction in mortality rate among the patients (8).

In other studies, mortality was numerically, but not statistically significantly, higher in the levosimendan group, with 45 (15%) deaths in the levosimendan group and 35 (12%) in the placebo group during the 90- day study period ($p=0.21$) (19). In the SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support) study, there was no significant difference in

survival between levosimendan and dobutamine (26% vs 28%; p=0.40) (20). On the contrary, mortality at 31 days was significantly lower with levosimendan than with dobutamine (p=0.046) (21).

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