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EFFECT OF LEVOSEMINDAN ON OUTCOME OF CORONARY ARTERY BYPASS GRAFTING SURGERY IN PATIENT WITH IMPAIRED LEFT VENTRICULAR SYSTOLIC FUNCTION

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ORIGINAL ARTICLE

Effect of Levosimendan on Outcome of Coronary Artery Bypass Grafting Surgery in Patient With Impaired Left Ventricular Systolic Function

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Abstract

Background: **Coronary artery bypass grafting (CABG) is often complicated by hemodynamic instability, especially in cases with decreased left ventricular ejection fraction (LVEF). Levosimendan as an inotropic agent can be used in those patients.**

Objective: **The aim was to assess morbidity and mortality rates up to 6 months following CABG surgery in patients with LVEF equals 35%, who were given levosimendan.**

Patients and methods: **A total of 40 patients with preoperative LVEF less than or equal to 35% who underwent elective CABG were retrospectively analyzed between March 2020 and April 2022 at Al-Azhar University Hospitals. Levosimendan was u continuously given as a bolus-free infusion at a rate of 0.05—0.2 μg/kg/min before surgery. Hemodynamic and outcome parameters were registered and statistically analyzed.**

Results: **A significant improvement was recorded in ejection fraction percentage from 32.8 to 35.9% and then 39.4% after 1 week and 6 months, respectively; it was associated with significant increase in cardiac output from 5.22 to 6.3 l/min and 6.1 l/min after 1 week and 6 months, respectively. Mean arterial pressure was also increased from 63.44 to 80.4 mm Hg and 84.6 mm Hg after 1 week and 6 months, respectively. Overall, 80% of patients showed no complications, whereas 5% of them had low cardiac output syndrome, 5% needed intra-aortic balloon pump (IABP), 5% rapid atrial fibrillation, and 5% needed reoperation due to bleeding. On the contrary, postoperative (later) complications included the following: severe sternal wound infection in two cases (5%) and chronic atrial fibrillation in one case (2.5%). The overall mortality rate was 10%.**

Conclusion: **Levosimendan has a beneficial effect in improving hemodynamic state. In addition, it aids the reduction of hospital and ICU stays, along with the ability to reduce the incidence of low cardiac output syndrome and mortality rate.**

Keywords: CABG, Levosimendan, LVEF

1. Introduction

Hemodynamic instability frequently complicates coronary artery bypass grafting (CABG) surgery, particularly in cases that have decreased left ventricular ejection fraction (LVEF).[1] An independent risk factor for mortality is preoperative left ventricular dysfunction. It is also linked to postoperative low cardiac output syndrome (LCOS). This illness can cause considerable morbidity and mortality if undiagnosed or mistreated.[2]

As a first line of therapy, inotropic drugs are used to treat LCOS. Unfortunately, the majority of inotropic substances either cause negative adverse effects or represent unknown safety risks. Therefore, researchers are looking for new medications with less harmful adverse effects.[3]

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Hence, the calcium-sensitizing action of levosimendan is connected to a beneficial inotropic effect, that is, myocardial contractility is increased. However, unlike other inotropes, it did not increase cyclic adenosine or intracellular calcium, which prohibited it from raising myocardial oxygen consumption, which tends to be beneficial for people with poor LVEF.[4-6]

Levosimendan can also help postoperative LCOS patients with their renal function, according to the study by Orriach et al.[7] This shows us that levosimendan can help people who already have LCOS, in addition to lowering the occurrence of the condition. These benefits are supposed to broaden the drug's potential applications.[7]

However, the use of levosimendan in cases with severely decreased LVEF was not proven to have any positive effects by Landoni *et al.*[8] Mehta *et al.*[9] Desai *et al.*[10] Wang *et al.*[11] and Van Diepen et al.[12] The positive benefits of levosimendan are still up for discussion in clinical settings.

Therefore, our study's aim was to assess the morbidity and mortality rates within 6 months following CABG surgery in cases with LVEF35% who had used levosimendan.

2. Patients and methods

A total of 40 patients with LVEF35% who underwent elective CABG at Al-Azhar University Hospitals between March 2020 and April 2022 were included in this prospective randomized trial.

All participants got thorough information on the study's goal and anticipated advantages. The entire project was conducted with the utmost ethical attention. Additionally, the approvals from the Faculty of Medicine's Ethical Committee and Institutional Review Board were obtained. All participants provided written consent after being fully informed; confidentiality related to their information was guaranteed.

Exclusion criteria were patients with LVEF% greater than 35; those with advanced hepatic, renal, or neurological diseases; terminal malignancy; severe form of chronic obstructive pulmonary disease; redo cases; extensive peripheral vascular disease; and patients with previous stroke.

All patients were subjected to the following: preoperative clinical evaluation, which included age, sex, general and local cardiological examination, and New York Heart Association classification.

Moreover, complete laboratory examinations, ECG, echocardiographic assessment, and coronary angiography were done.

Myocardial viability tests were performed to evaluate and assess myocardial viability and whether there are hibernating myocardium tissues with impaired flow or function; nevertheless, it is still viable and is expected to gain benefit from the surgery.

2.1. Operative

All patients were given a bolus-free infusion of levosimendan continuously at a rate of 0.05–0.2 μg/kg/min before surgery.

A total of 63 patients (males and females) were included in our study; they underwent elective, isolated, on pump CABG for disease of three vessels (final number of grafts were not taken into account) with the help of antegrade blood-enriched cardioplegic arrest under controlled hypothermia (28–32 °C).

The following data were registered:

Type of surgery off pump or on pump.

Cardiopulmonary bypass (CPB) time in minutes.

Aortic cross-clamp time in minutes.

Difficulty of weaning from bypass.

Total operative time from skin incision to skin closure.

Operative complications.

Type of inotropic and mechanical support such as intra-aortic balloon pump (IABP).

Operative mortality if found.

2.2. Postoperative

Evaluation of hemodynamics.

Types and doses of inotropes.

Total amount of blood loss in ml.

Total of consumed units of packed red blood corpuscles (RBCs), fresh frozen plasma (FFP), and platelet transfused.

Duration of mechanical ventilation in hours and any re-ventilation cause and duration.

Duration of hospitalization (ICU and hospital).

Causes and duration of ICU readmission.

Echocardiography for assessment of ejection fraction (EF), and wall motion abnormalities.

2.3. Outcome

In-hospital mortality.

Complications such as arrhythmias, cerebrovascular stroke, reoperation, infection, previous myocardial infarction, renal or liver impairment, and gastrointestinal tract complications.

2.4. Follow-up

The follow-up was done in the first week and then 6 months after the surgery for morbidity and mortality.

Echocardiographic follow-up was conducted for assessing cardiac function and wall motion abnormality.

2.5. Statistical analysis

Our data were processed with the help of Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, Illinois, USA). For quantitative measures, mean and SD were employed, but for qualitative parameters, number and percentage were employed. The means of one or more variables based on repeated observations of normally distributed variables were compared using the analysis of variance test.

If the *P* value was less than 0.05, it was deemed significant.

3. Results

A total of 40 consecutive patients with severe LVEF (≤35%) had an elective CABG during the course of this research. Their mean age was 61.1 ± 4.7 years. Overall, 80% of them were males.

Table 1 presents the demographic, comorbidities, and clinical data among studied cases.

Table 2 presents preoperative echo findings. The mean ± SD LVEF, left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) of studied cases were 32.8 ± 1.2%, 6 ± 0.22, and 4.5 ± 0.41, respectively. Overall, 42.5% of cases had diastolic dysfunction grades I and II.

Table 1. Distribution of the studied cases according to descriptive analysis, comorbidities, and clinical data.

Variable	Value [*n* (%)]
Age (years) [mean (range)]	61.1 (50–68)
Sex: males	32 (80)
Associated risk factors	
Diabetics	18 (45)
Hypertension	8 (20)
Hypertension and diabetic	8 (20)
Hyperlipidemia	11 (27.5)
Obesity	18 (45)
Previous MI	6 (15)
NYHA classification	
NYHA class II	17 (42.5)
NYHA class III	23 (57.5)
Chest radiography	
Cardiomegaly	2 (5)
Pulmonary congestion	2 (5)
Bronchopneumonia	2 (5)

MI, myocardial infarction; NYHA, New York Heart Association.

Table 2. Distribution of the studied cases according to preoperative echocardiographic findings among cases.

Variable	Value
Postoperative echocardiography (mean ± SD)	
LVEF (%)	32.8 ± 1.2
LVEDV	106 ± 11.2
LVESV	54.2 ± 7.41
Diastolic dysfunction [*n* (%)]	
Grade II	17 (42.5)
Grade III	17 (42.5)
Mitral valve disease [*n* (%)]	
Moderate MR	5 (12.5)
Severe MR	2 (5.0)
Viability tests [*n* (%)]	
Thallium SPECT	2 (5)
Dobutamine stress test	5 (12.5)
Cardiac MRI	2 (5)

LVEF, left ventricular ejection fraction.

Table 3. Distribution of the studied cases according to operative data among studied cases.

Variable	% = 100
Surgical technique [*n* (%)]	
On pump CABG 3 graft	32 (80)
On pump CABG 4 grafts	6 (15)
On pump CABG 4 grafts ± MV replacement	2 (5)
Total operative time (min) (mean ± SD)	230 ± 45.9
Total CPB time (min) (mean ± SD)	117.7 ± 27.9
Cross-clamp time (min) (mean ± SD)	69.5 ± 8.5
Inotropes [*n* (%)]	
Levosimendan	40 (100)
Adrenaline	30 (75)
Noradrenaline	38 (90)
Dobutamine	4 (10)

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

Five cases (12.5%) presented with moderate mitral regurgitation (MR) and were treated by dobutamine stress echocardiography, and two cases (5%) presented with severe MR that were managed by mitral valve (MV) replacement. Regarding myocardium viability tests, two, five, and two cases were positive for thallium single-photon emission computerized tomography (SPECT), dobutamine stress test, and cardiac MRI tests, respectively.

Table 3 shows that 80% of cases had on pump CABG 3 graft, 15% of them had on pump CABG 4 grafts, and 5% of them had on pump CABG 4 grafts with MV replacement. The mean total bypass and aortic cross-clamp times were 117.7 ± 27.9 and 69.5 ± 8.5 min, respectively. All patients received levosimendan (0.05–0.2 μg/kg/min) 24 h before operation, and then continued the maintenance doses during intraoperative and postoperative times. This was in line with giving adrenaline for 30 (75%) of cases, noradrenaline in 38 (90%), and dobutamine in four (10%) of cases.

Table 4. Blood product usage, mechanical ventilation, ICU stay, and hospital stay among studied cases.

Variable	Mean ± SD	Range
Blood product usage		
Blood loss (ml)	461.1 ± 133.7	350–900
Packed RBCs	2 ± 0	2–2
FFP	2.7 ± 0.76	2–4
Platelets	0	0
Ventilation (h)	8.1 ± 1.3	8–10
ICU stay (h)	50.5 ± 2.8	58–55
Hospital stays (days)	7.1 ± 0.53	6–8

FFP, fresh frozen plasma; RBC, red blood corpuscle.

Table 5. Postoperative complications among studied cases.

Variable	% = 100
Early postoperative complications [*n* (%)]	
LCOS	2 (5.0)
Needing for IABP	2 (5.0)
Rapid AF	2 (5.0)
Reoperation due to bleeding	2 (5.0)
Late postoperative complications [*n* (%)]	
Sternal wound infection	2 (5.0)
Chronic AF	1 (2.5)
Mortality	4 (10)
Postoperative echo (mean ± SD)	
Inpatient EF (%)	35.9 ± 1.9
First week mean PG on MV	0.27 ± 1.2
Six-month follow-up echo	39.4 ± 13.8
EF (%)	
LVEDV	105.5 ± 8.38
LVESV	54.3 ± 6.39

AF, atrial fibrillation; EF, ejection fraction; LCOS, low cardiac output syndrome; PG, pressure gradient.

Table 4 shows that the mean blood loss of studied cases was 461.1 ± 133.7 ml, which ranged from 350 to 900 ml. The mean ± SD packed RBCs and FFP were 2 and 2.7 ± 0.76 unit, as a replacement therapy, respectively. Mechanical ventilation ranged from 8 to 10 h, with mean ± SD of 8.1 ± 1.3 h. ICU and hospital stays were 50.5 ± 2.8 h and 7.1 ± 0.53 days, respectively.

Table 5 presents postoperative complications. Overall, 80% of them had no complications, whereas 5% had LCOS, 5% had rapid atrial fibrillation (AF), 5% needed IABP, and 5% required reoperation owing to bleeding. Additionally, two cases (5%) had severe sternal wound infection, and one case (2.5%) had chronic AF later on. Hospital mortality was recorded in four cases (10%); they were male patients, diabetic, hypertensive, and obese who were admitted with typical ischemic chest pain. EF was less than 30% with severe hypokinesia of apex of the heart and septum. Coronary angiographic data revealed left main coronary artery with distal subtotal occlusion in two patients, and multivessel coronary disease in other two patients. They underwent CABG 3 graft which had taken long intraoperative and bypass time. Two patients were shifted to ICU with unstable hemodynamic status; they were put on high inotropic support and levosimendan. Another two cases were complicated by deep sternal wound infection and mediastinitis. Regarding postoperative echo, the mean inpatient EF percentages of studied cases were estimated as 35.9 ± 1.9, whereas the mean pressure gradient was 0.27 ± 1.2. After 6 months, EF % was recorded as 39.4 ± 13.8% (Fig. 1).

Table 6 shows significant improvement in EF% from 32.8 ± 1.2 to 35.9 ± 1.9% after 1 week, then to 39.4 ± 13.8% after 6 months. These changes were associated with significant increase in COP from 5.22 ± 0.6 to 6.3 ± 0.7 l/min and then 6.1 ± 0.7 l/min after 1 week and 6 months, respectively. Mean arterial pressure (MAP) was also increased from 63.44 ± 9.8 to 80.4 ± 10.3 mm Hg and 84.6 ± 11.2 mm Hg after 1 week and 6 months, respectively (Figs. 2–4).

4. Discussion

Levosimendan is a drug that protects against ischemia and heart damage driven by the ischemia reperfusion phenomenon; it acts by increasing calcium's sensitivity to troponin C.[1] Levosimendan had a positive effect on weaning from MV, as seen by lower mean CPB and aortic cross-clamp (ischemia) times in the current trial (117.7 and 69.5 min, respectively), shorter hospitalization days (7.1 ± 0.53 days), shorter ICU stays (50.5 ± 2.8 h), and less mechanical ventilation times (8.1 ± 1.3 h). Recently, Kaltsi and colleagues presented the findings of a pilot study on the use of levosimendan in participants with LVF who were weaned from MV; these findings are similar to the current work. In other work by Jiménez-Rivera and colleagues, they tried to compare 13 participants having LVEF 40%, who were involved in prospective treatment with continuous levosimendan infusion (dosage: 0.05–0.2 g/kg/min free-of-loading dose which was started 48 h prior to surgery), against 41 participants, labeled as retrospective controls. They discovered a significant association between the use of levosimendan and a considerably shorter MV time and ICU stay ($P = 0.03$).[13]

The findings of Al Jawad and Shorbagy[14] were also consistent with the current study, which showed that levosimendan was linked with less ICU stays, fewer hours spent on mechanical breathing, and fewer needs for mechanical assistance. Additionally, Na et al.[1] found that the levosimendan group experienced a postoperative reduction in ICU and hospital stays.

The hemodynamic effects of levosimendan are satisfactory, even with elevated risks related to the surgical approach. The current study reported only

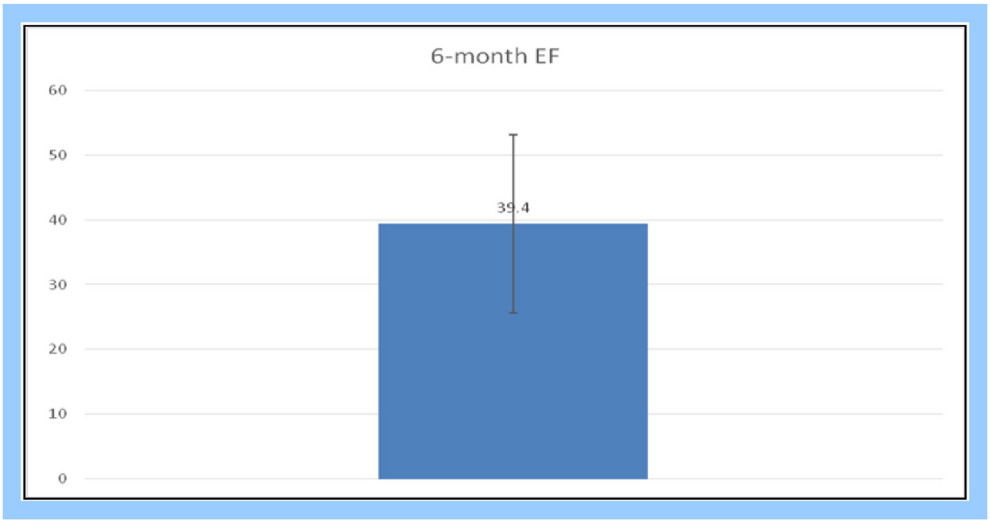

Fig. 1. Six months ejection fraction (EF) among the studied cases.

Table 6. Comparison between preoperative and follow-up EF among the studied cases.

Variable	Preoperative	First week	Six months	*P* value[a]
EF (%) (mean ± SD)	32.8 ± 1.2	35.9 ± 1.9	39.4 ± 13.8	0.000
Cardiac output, l/min (mean ± SD)	5.22 ± 0.6	6.3 ± 0.7	6.1 ± 0.7	0.000
MAP, mm Hg (mean ± SD)	63.44 ± 9.8	80.4 ± 10.3	84.6 ± 11.2	0.000

EF, ejection fraction; MAP, mean arterial pressure.
[a] Repeated measure analysis of variance test.

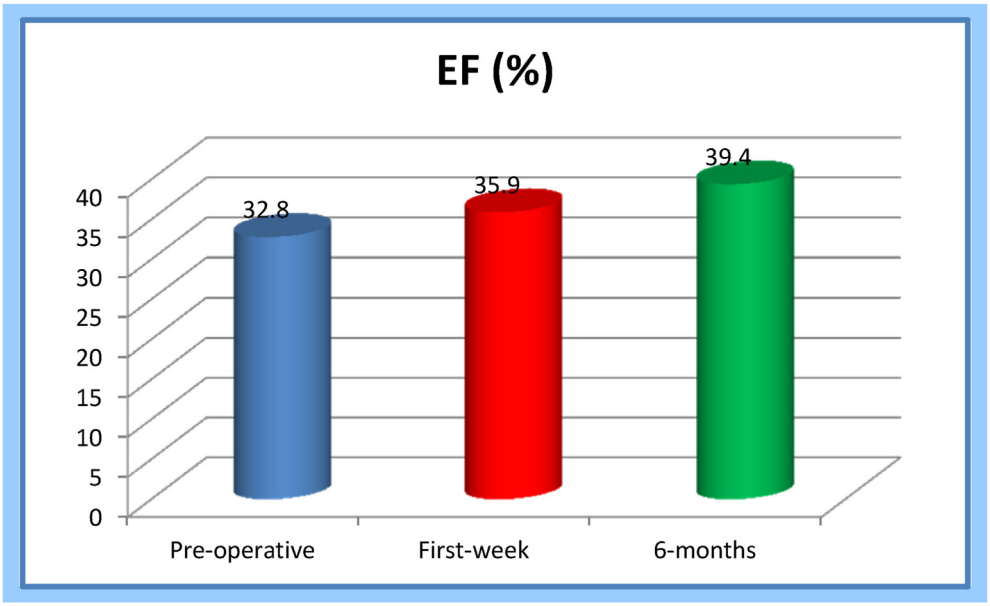

Fig. 2. Ejection fraction (EF%) in preoperative and follow-up among the studied cases.

two LCOS cases (5%) of the recruited patients. This study implies that, levosimendan may be beneficial for patients whose LVEF has been drastically diminished as a result of poor contractility.

In contrast to the current investigation, Na et al.[1] discovered that 21% of patients had LCOS when they were in the postoperative period. After propensity score matching, their analysis found that

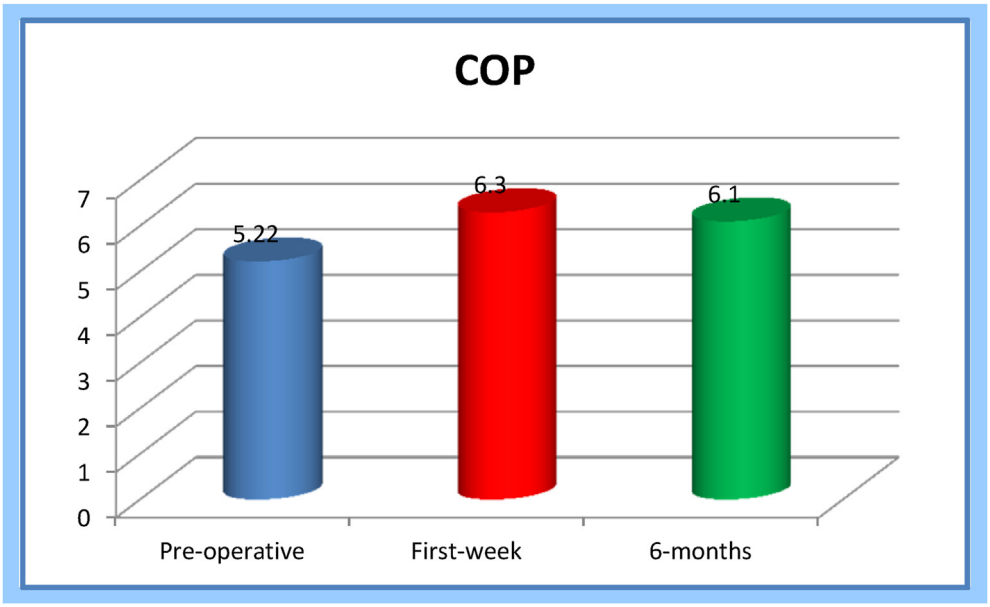

Fig. 3. Cardiac output in preoperative and follow-up among the studied cases.

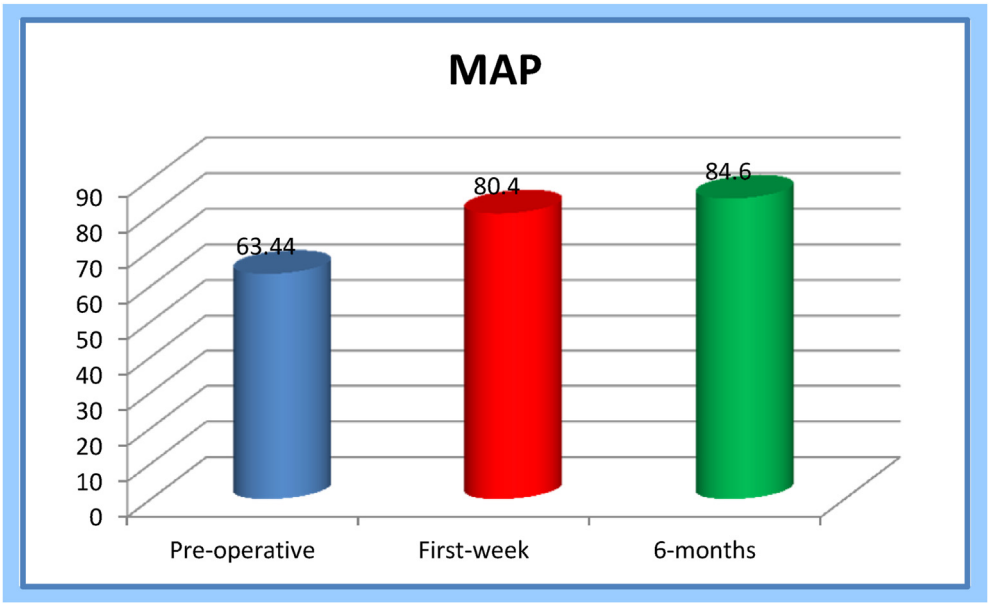

Fig. 4. Mean arterial pressure (MAP) in preoperative and follow-up among the studied cases.

exposure to levosimendan was the only factor that was still significantly linked to a lower incidence of LCOS.

Levosimendan has an effect on AF, as evidenced by the two cases (5%) of postoperative fast AF that occurred in those who were included in the study.

Levosimendan was linked to a lower incidence of arrhythmia after the surgery, according to the study by Al Jawad and Shorbagy,[14] which is comparable to our findings.

Along with having fewer postoperative problems and requiring fewer packed RBCs and FFP, pre-conditioned patients also spent less time in the ICU, which is consistent with findings from other related studies by Tritapepe et al.[15] and Wang et al.[16]

In contrast, Gandham and colleagues found that patients undergoing cardiac surgery who were on

levosimendan had a greater need for inotropes, particularly vasopressors. Both levosimendan and dobutamine were tested for their effect on participants undergoing MV surgery as they were weaned from CPB. Levosimendan administration has been shown to be 'better timed' by many authors to reduce both the following: damage of the myocardium, the need for inotropes and vasopressors, as well as the need for mechanical assistance. The majority of researches concur that it is advantageous to provide levosimendan preoperatively 12–24 h before CPB.[15,17]

According to the current study, after 1 week then 6 months, the EF% significantly improved from 32.8 ± 1.2 to 35.9 ± 1.9% and 39.4 ± 13.8%, respectively; these alterations were linked to a considerable increase in cardiac output, which went from 5.22 l/min to ~6.3 l/min and 6.1 l/min, respectively. Additionally, MAP raised from 63.44 to 80.4 and 84.6 mm Hg after 1 week then 6 months, respectively.

In line with what we found, Beiras-Fernandez and colleagues found that EF% dramatically increased from 27.4 to 38.8% and 45.10% within 24 and 48 h of initiating levosimendan, respectively. Additionally, during the timespan of the 48 h, the MAP showed a consistent and a statistical significant increase, going from 67 to 10 to 80–9 and subsequently to 83–9 mm Hg ($P = 0.05$).

The MPAP simultaneously decreased from 317 mm Hg preceding levosimendan to 246 within the first 24 h after levosimendan initiation. These disparities could not be supported by statistics. Moreover, the CO rose statistically over the course of the first 24 h from 5.2 ± 0.6 l/min at the beginning of therapy to 6.2 ± 0.7, then slightly decreased over the course of the next 24-h duration to 5.9 ± 0.6 l/min.[18]

The significant improvement in our participants' EF, which occurred within and after infusion of levosimendan, has been show in a number of earlier studies, by Di Molfetta et al.[19] and Beiras-Fernandez *et al.*[18] including cardiac surgery patients. When attributing an increase in the EF to a single component of a comprehensive treatment strategy, it is important to take into account the sophistication of the hemodynamic factors involved in recovering from heart surgery.

An important clinical outcome for patients who are critically sick is mortality as a primary result. In the current investigation, four cases (10%) of death were reported. They were admitted as male patients with typical ischemic chest discomfort who were also diabetic, hypertensive, and obese. The septum and apex of the heart both had severe hypokinesia, and the EF% was less than 30. Two patients had left main coronary artery distal subtotal blockage on coronary angiography; on the contrary, another two cases had multivessel coronary disease. They had a CABG 3 graft, which requires a lengthy bypass and intraoperative period. Two patients who had been transferred to the ICU were receiving a high-support inotropic dose and levosimendan. Deep sternal wound infection and mediastinitis had aggravated the cases of the other two individuals.

According to multiple studies, levosimendan had showed a mortality benefit when compared with other medications in patients undergoing heart surgery[16,20-23]

Sanfilippo et al.[24] assessed the effects of levosimendan in low-EF patients or LCOS, in a published meta-analysis in 2017 and discovered that only the subgroup with 35%EF showed lower mortality. Wang and colleagues evaluated the outcomes of levosimendan infusion in 59 patients with acute-decompensated HF. At the 1-month follow-up, one reported death and one documented readmission had occurred in each group.[16]

In addition, Allama and colleagues found that although three patients died in the IABP group, one patient did not survive the bypass, other patient acutely suffered from renal insult and passed away after 5 days postoperatively, and the last patient suffered from septicemia. Of the four patients who died in the control group, two failed to survive the bypass while the other two deaths were attributed to multiorgan failure related to LCOS. Two patients in the levosimendan group passed away; one did not successfully exit the bypass, and the other passed away due to hemodynamic instability on day 1 after surgery. There were no differences of statistical significance between the studied groups.[25]

Three recent clinical trials published by Landoni *et al.*[8] Mehta *et al.*[9] and Cholley et al.[26] did not show improvement over mortality, which came in contrast in contrast with our findings.

Elbadawi et al.[27] performed a meta-analysis to evaluate prophylactic levosimendan shots in patients having heart surgery; however, no statistically significant changes in mortality within 1 month were discovered. A total of 60 patients, who were recognized with LVEF35% preoperatively, were randomly allocated after having either valvular surgery, CABG, or aortic aneurysm operation to obtain levosimendan ($n = 30$), or to obtain conventional inotropes and vasoactive regimens in a prospective observational research carried out by Khaled et al.[28]

The loading dosage of levosimendan that was given initially ranged from 6 to 12 g/kg over 0.5 h. Although there were no detected mortality

disparities among the groups, levosimendan improved LVEF ($P = 0.002$ versus the control group) and caused other hemodynamic changes that were in line with the drug's known profile (9 deaths vs. 10).[28]

Oliveros and colleagues concluded in their systematic review and meta-analysis that levosimendan administration in patients after CVS surgery had no effect on mortality within 30 days. The prevention of postoperative kidney failure was achieved by dialysis.[3] Although the duration of ICU stay was shorter in the levosimendan group (4.4 vs. 5.2 days), the primary findings from an RCT by Omar et al.[29] in 279 patients, who were presenting with LVEF35% and underwent CABG surgery, uncovered no mortality rate differences of significance between those who were given 0.1 g/kg/min 24-h levosimendan and those allowed to an IABP.

The results could be affected by a variety of confounding variables, including baseline features of the patient, preexisting conditions, drugs, or the surgeon's background. This strategy also prevents levosimendan from being used as a last resort; it also prevents delaying its administration until organ failure takes place in addition to failure of all other measures. Our therapeutic algorithm also makes sure that levosimendan is used in a regulated and established way quickly following the development of postoperative LCOS.

4.1. Conclusion

In high-risk patients, levosimendan enhances hemodynamics and enables weaning off CPB perioperatively. Beside reducing the requirement for catecholamines and mechanical circulatory support, it also secures shorter hospitalization periods.

Conflict of interest

Authors declare that there is no conflict of interest, no financial issues to be declared.

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