The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89, Page 4155-4164

Evaluation of Levosimendan in Patients with High Risk Severe Mitral Valve Disease Undergoing Mitral Valve Surgery

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ABSTRACT

Background: Levosimendan has anti-ischemic effects, improves myocardial contractility and increases systemic, pulmonary and coronary vasodilatation.

Objectives: The present study investigated the perioperative hemodynamic effects of a prophylactic infusion of levosimendan in high-risk mitral valve surgery patients with left ventricle dysfunction, and compared short-term clinical outcomes with a control group in which levosimendan wasn't used.

Patients and methods: Between October 2019 and May 2021, a prospective randomized clinical study was performed in 100 patients with high-risk mitral valve surgery with left ventricular dysfunction and pulmonary hypertension. In the study group, patients received levosimendan infusion at a dose of 0.1 mcg/kg/min after the induction of anesthesia while in control group levosimendan was not used. The intraoperative and postoperative data were recorded for each patient in both groups. The hemodynamic measurements were performed at six predetermined time points (0, 1, 6, 12, 24 and 36 hours postoperatively).

Results: Levosimendan had significantly improved postoperative hemodynamic values. It improved mean arterial pressure at different times postoperatively ($p < 0.05$), heart rate at different times postoperatively ($p < 0.05$). Also, levosimendan preserved LV systolic performance postoperatively (pulmonary artery pressure (PAP): 51.7 ± 6.4, 57.9 ± 8.6, P<0.001) and (ejection fraction (EF): 37.1 ± 9.3, 33.4 ± 7.1, P=0.03).

Conclusion: Prophylactic levosimendan improved the hemodynamics in high-risk mitral valve surgery patients. So levosimendan seems to be a safe and effective choice for preventing left ventricular failure in high-risk mitral valve surgical patients with LV dysfunction.

Keywords: Left ventricular dysfunction, Levosimendan, Mitral valve surgery, Pulmonary hypertension.

INTRODUCTION

Many individuals who are candidates for cardiac surgery today are at significant perioperative risk for increased morbidity and death. Pulmonary arterial hypertension and poor ejection fraction are two significant risk factors influencing surgical outcome in patients with mitral valve dysfunction. Individually or in combination, the presence of these risk factors may make weaning off cardiopulmonary bypass (CPB) difficult and may result in severe left and right ventricular failure following CPB [(1, 2)].

Myocardial stunning, anesthetic drugs, vasodilation, and hyperthermia generated by the inflammatory response associated with CPB are all factors that contribute to hemodynamic instability in the early postoperative period [(3)]. The recovery from this phenomena begins one hour (h) after the CPB is terminated and lasts for 24 hours [(4)].

Treatment methods for patients who cannot be weaned from CPB or develop low cardiac output after CPB include use of inotropic agents, vasodilators, intra-aortic balloon pump, insertion of a balloon pump into the pulmonary artery, implementation of right ventricular assist devices and extracorporeal membrane oxygenation. Levosimendan, a recently introduced calcium sensitizer, exhibits positive inotropic activity by increasing the ionized calcium sensitivity of cardiac troponin C and facilitating calcium binding to the myofilaments. Additionally, it exhibits vasodilator effects on the decrease in intracellular calcium level by allowing the ATP-sensitive potassium channels to be opened[(5)].

Levosimendan differs from other positive inotropic drugs with features such as increasing contractility without increasing myocardial oxygen consumption, improving coronary perfusion with its vasodilator activity, reducing preload and afterload by vasodilatation in the pulmonary, renal, splanchnic, cerebral and systemic arteries as well as in the saphenous, portal and systemic veins [(6, 7)].

This study was designed to evaluate the effect of levosimendan in patients with mitral valve disease undergoing high risk mitral valve surgery in comparison with using only the standard care, regarding postoperative prognosis, hemodynamics, morbidity and mortality.

PATIENTS AND METHODS

This prospective randomized controlled study was performed at Cairo University and Fayoum University Hospital in Egypt in the period between October 2019 and May 2021.

Population of study and disease condition:

One hundred patients who presented with severe mitral valve disease identified by clinical data and preoperative echocardiography who needed high risk mitral valve replacement surgery were included. The patients were divided into two groups, 50 patients each; in Group A patients received levosimendan

Received: 22/03/2022
Accepted: 19/05/2022

(levosemidan group) while in Group B patients didn't receive this drug (control group).

Inclusion criteria: Severe mitral valve disease (stenosis, regurge or double lesion), impaired left ventricular function (EF <50%), severe pulmonary hypertension (PAP ≥ 60), and symptomatic patients (New York Heart Association (NYHA) class III, IV) despite maximum medical treatment.

Exclusion criteria: Associated moderate or severe aortic valve disease, undergoing combined mitral valve surgery with coronary artery bypass graft, renal dysfunction (serum creatinine >2 mg/dl and/or chronic kidney disease), re-exploration for surgical causes, and redo cardiac surgery.

Methodology in details:

We divided 100 patients randomly into 2 groups: Levosimendan group (n = 50) and control group (n = 50). All patients were to undergo mitral valve replacement.

In the study group, patients received levosimendan infusion at a dose of 0.1 mcg/kg/minute after the induction of anesthesia while in control group levosimendan was not be used. Additional inotrope and/or vasoconstrictor might be used based on hemodynamic parameters.

All patients in this study were evaluated by the following parameters:

Preoperative:

A. Complete history taking and clinical examination:

- With special emphasis on age, sex, body surface area and history of previous ICU admission.
- Physical examination for exclusion of any co-morbidity.
- Patients underwent thorough clinical evaluation, which included clinical examination and imaging, which determined the associated risk profile of these patients; the following findings were considered high risk criteria (history of ICU admission, signs of heart failure, comorbidities and chest X-ray findings of congested lung or pleural effusion).

B. Laboratory Investigations:

- Complete blood count to assess the preoperative hemoglobin.
- Liver and kidney function tests.
- Coagulation profile.
- Blood sugar, if diabetic (fasting blood glucose level, 2 hours post prandial blood glucose level, HBA1C) proper control of diabetes before surgery was done with a consultation of internal medicine specialist.

C. Chest X-ray: for chest congestion and other signs of heart failure.

D. ECG: to detect preoperative atrial fibrillation.

E. Echocardiography:

- Detailed description of mitral valve pathology, mitral valve area.
- Pulmonary artery pressure measurement.
- LV dimensions (end diastole, end systole).
- Left ventricular ejection fraction.

Preoperative preparations:

All patients received the morning dose of cardiac medications. Intramuscular 10 mg morphine sulfate before transfer to operating room.

After arrival in the preparation room a 14-gauge peripheral cannula was inserted using local anesthesia. Sedation was optimized using 0.03-0.07 mg/kg midazolam. A 20 gauge non-dominant radial artery cannula was inserted using local anesthesia. Two blood samples were withdrawn from the arterial line, the 1st for preoperative baseline activated clotting time (ACT) and the 2nd sample for baseline arterial blood gas (ABG) analysis on fraction of inspired oxygen (FIO_2) 21%. Monitoring started preoperatively using five leads ECG, direct arterial blood pressure and pulse oximetry.

Intraoperative period:

A) Anesthesia technique: The intraoperative anesthesia technique was the same for all patients and consisted of fentanyl 5-10 mg/kg and endotracheal intubation was facilitated with the use of pancuronium 0.02 mg/kg. Additional dose of 100-200 µg was given in on need base, after full muscle relaxation, the trachea was intubated orally with an appropriately sized endotracheal tube. Anesthesia in all patients was maintained with inhalation. After induction, a triple lumen central line venous catheter, urethral catheter and nasopharyngeal temperature probe were also inserted. Levosimendan infusion at a dose of 0.1 mcg/kg/minute without loading dose was started through central venous line in the half of the patients after the induction of anesthesia (levosimendan group).

B) Surgical technique: Mitral valve replacement (MVR) was performed through median sternotomy. Surgery was performed on CPB (aorto-bicaval cannulation) with moderate hypothermia (28°C to 32°C) and intermittent cold blood cardioplegic cardiac arrest at every 40 min. Mitral valve replacement was performed using appropriate size of the prosthetic valve through left atriotomy with preservation of posterior leaflet and related subvalvular apparatus. Weaning of cardiopulmonary bypass after metabolic optimization and addition of other appropriate pharmacological support according to the hemodynamic status of the patient was done. CPB and cross clamp time were recorded. Hemostasis and closure were performed.

C) Operative parameters were recorded: CPB and aortic cross clamp time (minutes). Need for other

inotropes (which inotrope and the dose of it): Defined as inotropes added in operating room (OR) and continued beyond the time of transfer to ICU, and noradrenaline was titrated to target mean arterial pressure (MAP) of 70 mmHg or greater.

Postoperative:

- Weaning from inotropic drug support was at the discretion of the attending intensivist in the ICU and was based on the assessment of hemodynamic data, urine output, ABG, and the patient's physical status. These physicians were not involved in the collection or the interpretation of the study data.

Duration of mechanical ventilation (hours):

Weaning from mechanical ventilation and tracheal extubation followed a standard protocol using the following criteria: temperature >36°C, stable hemodynamics, chest tube drainage <100 mL/h, and urine output ≥0.5 ml/kg/h. Patients received morphine 0.2 mg/kg and paracetamol 1 g. Fifteen minutes later, the patient was extubated when the following criteria were achieved: adequate obeying to command, $SpO_2 \geq$ 95% at $FiO_2 \leq 0.5$, pH ≥ 7.3, $PaCO_2 \leq$ 55 mm Hg, and respiratory rate <30 bpm.

ICU stay (days): Patients were discharged from the ICU when the following criteria were met: $SpO_2 \geq 90\%$ at $FiO_2 \leq 0.5$ by facemask, stable hemodynamics, chest tube drainage <50 mL/h, urine output >0.5 ml/kg/h, no IV inotropic or vasopressor therapy for at least 12 hours.

Hospital stay (days): The criteria for hospital discharge were hemodynamic stability, no wound discharge, no fever, ability to void and move bowels, and ability to independently ambulate and self-feed.

Hemodynamic variables recording: Mean arterial blood pressure (MAP), central venous pressure (CVP) and heart rate (HR) at time of ICU admission, one hour, 6 hours, 12 hours, 24 hours and 36 hours postoperative.

Echocardiography (one week postoperative): with evaluation of ejection fraction, RV function, LV dimensions, pulmonary artery pressure, prosthetic valve function.

Mortality.

Potential risks:

Adverse reactions associated with levosimendan therapy include:

Headache, hypotension (due to vasodilatation), arrhythmias (atrial fibrillation, extra systoles, atrial tachycardia, ventricular tachycardia), myocardial ischemia, and hypokalemia and/or nausea.

Any of these side effects if uncontrolled medically, the drug was discontinued.

Study outcomes:

Primary outcomes: Incidence of postoperative heart failure, and mortality.

Secondary outcome: Incidence of postoperative ventricular stunning, and length of ICU and hospital stay.

Ethical consent:

An approval of the study was obtained from Cairo and Fayoum University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using the Statistical Package for the Social Sciences **(**SPSS) software version 22 in windows 7 (SPSS Inc., Chicago, IL, USA). Simple descriptive analysis in the form of numbers and percentages of qualitative data, and arithmetic means and standard deviations of quantitative parametric data. Quantitative data included in the study were first tested for normality by one-sample Kolmogorov-Smirnov test and then were compared by independent samples t test. Chi square test used to compare qualitative data. The P-value< 0.05 was considered significant.

RESULTS

Preoperative data:

The mean age of the studied patients was 39 ± 13.5 years in group A (levosimendan group) and 42 ± 9.87 years in group B (Control group) (Table 1)**.**

Table (1): Comparison of demographic data among two studied groups

Variables	**Group A** (n=50)	**Group B** (n=50)	p-value
Demographic data			
Sex			
Females	28 (56%)	31 (62%)	0.54
Age (years)	39 ± 13.5	42 ± 9.87	0.21
Body surface area (m^2)	1.55 ± 0.21	1.59 ± 0.15	0.28

Table (2) illustrates that there was no statistically significant difference between the 2 groups as regard to preoperative risk profile.

Table (2): Comparison of the associated risk factors among both studied groups

Variables	Levosimendan Group (n=50)	Control group (n=50)	p-value
History of previous ICU admission	5 (10%)	6 (12%)	0.75
Signs of heart failure on admission	3 (6%)	5 (10%)	0.46
Comorbidities	7 (14%)	6 (12%)	0.77
Chest X-ray findings of HF	5 (10%)	4 (8%)	0.72
Atrial fibrillation	21 (42%)	18 (36%)	0.54

Table (3) illustrates that there was no statistically significant difference as regards to preoperative echocardiography findings between the 2 groups. The management of associated functional TR depended on the surgeon's preference and decision either band annuloplasty or tricuspid repair with ring or conservative management (with moderate functional TR).

Table (3): Comparison of the preoperative echocardiography among both study groups

Variables	Levosimendan Group (n=50)	Control group (n=50)	p-value
Pathology			
Stenosis	24 (48%)	27 (54%)	0.54
Regurge	11 (22%)	9 (18%)	0.61
Both	15 (30%)	14 (28%)	0.83
LVED	56.2 ± 9.4	54.7 ± 9.5	0.43
LVES	47.5 ± 6.3	47.3 ± 6.8	0.88
PAP	67 ±9.6	66 ±15.07	0.69
LVEF	37.6 ± 6.5	38.8 ± 6.7	0.37
Associated moderate to severe tricuspid regurge (TR)	21 (42%)	18 (36%)	0.54

Operative data:

Table (4) illustrates that there was a statistically significant difference between the two study groups as regards using noradrenalin as an inotropic drug with a higher percentage in levosimendan group (70%) versus (38%) in controls. On the other hand, there was no statistically significant difference regarding bypass time, cross clamp time and use of other inotropes.

Table (4): Comparison of operative variables in both study groups

Variables	Levosimendan Group (n=50)	Control group (n=50)	p-value
CPB time (min)	87.7 ± 9.8	89.5 ± 10.6	0.38
AXC (min)	47.4 ± 6.15	48.2 ± 5.84	0.51
Other inotropes			
– Adrenaline	27 (54%)	25 (50%)	0.69
– Noradrenaline	35 (70%)	**19 (38%)**	**0.001***
– Dobutamine	30 (60%)	32 (64%)	0.68
– Others	2 (4%)	7 (14%)	0.08

* = significant

Postoperative data:

All the patients were discharged to the cardiothoracic ICU, mechanically ventilated. Patients were discharged from the ICU when hemodynamically stable, no inotropic support, and no drains and with satisfactory postoperative laboratory results.

There was no statistically significant difference between the 2 groups, regarding ventilation time, ICU stay, and mortality.

Mortality- in both groups- was due to postoperative low cardiac output and hypoperfusion in spite of maximum inotropic support. One of them in the control group died during renal dialysis session (Table 5).

Table (5): Comparison of postoperative variables between both study groups

Variables	Levosimendan Group (n=50)	Control group (n=50)	p-value
Mechanical ventilation (h)	6.37 ±2.6	7.1 ±2.3	0.14
ICU stay (days)	3.24 ± 1.3	3.6 ± 1.13	0.14
Mortality	3 (6%)	5 (10%)	0.46

Intensive care unit course evaluation:

During ICU stay, the following data were collected from all patients in both groups and evaluated.

Hemodynamic variables at end of surgery in both study groups:

1) Heart rate:

Table (6) illustrates that concerning vital signs there was a statistically significant low mean of HR measures among levosimedan group at zero, 1, 6, 12, and 24 hours versus control group with no difference after 36 hours.

Table (6): Comparison of postoperative measured heart rate between both groups

HR	Levosimendan Group (n=50)	Control group (n=50)	p-value
0 h	96.2 ± 7.6	101.4 ± 6.3	**<0.001***
1 h	94.7 ± 8	100.5 ± 7.6	**<0.001***
6 h	89.7 ± 6.1	92.3 ± 4.9	**0.02***
12 h	85.2 ±5.9	82.6 ±4.3	**0.01***
24 h	90.2 ± 5.1	95 ± 5.5	**<0.001***
36 h	91.3 ±6.4	90.2 ± 5.5	0.36

* = significant

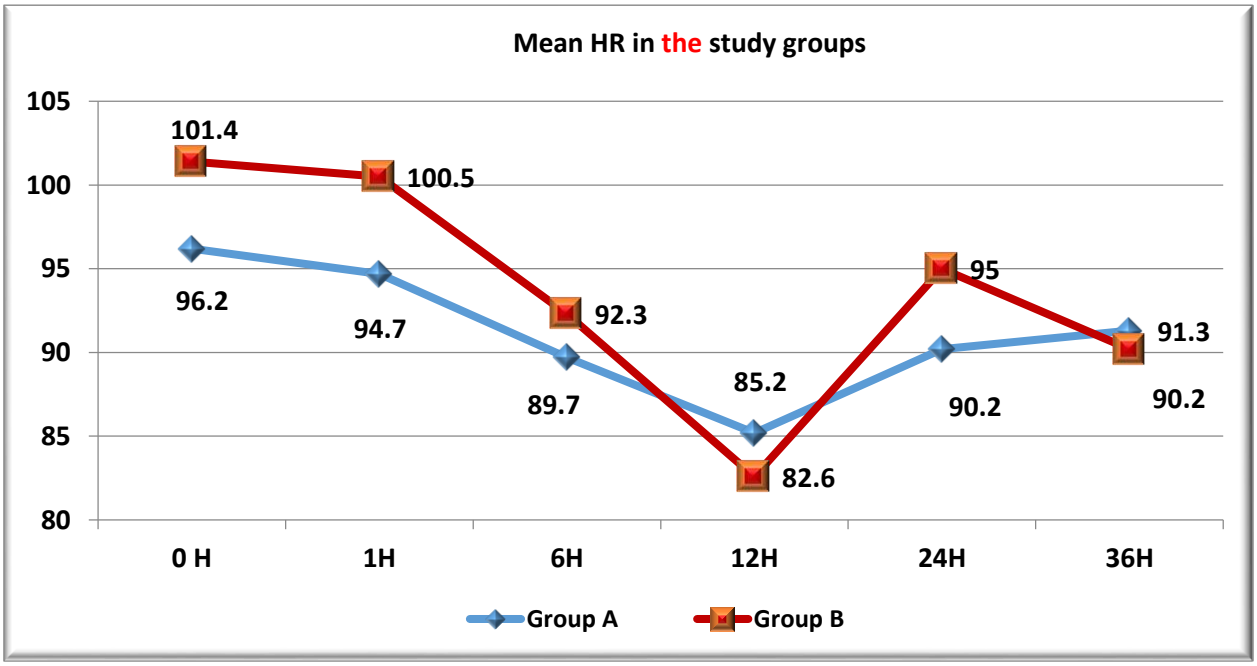

Figure (1): Mean HR in the study groups

Group A: levosimendan group, group B: Control group

2) Mean arterial pressure:

Table (7) illustrates that there was a statistically significant difference between the two study groups as regards MAP measures follow up with high mean of MAP among levosimedan group after 6, 12, 24, and 36 hours versus control group with no difference in MAP at zero, and 1 hours.

Table (7): Mean arterial blood pressure among both study groups at various time intervals postoperatively

MAP	Levosimendan Group (n=50)	Control group (n=50)	p-value
0 h	64.9 ± 5.3	63.3 ± 5.9	0.16
1 h	63.37 ± 5.1	65.3 ± 5.6	0.07
6 h	**72.4 ± 6.7**	64.8 ± 6.5	**<0.001***
12 h	**72.5 ± 5.8**	65.7 ± 7.3	**<0.001***
24 h	**73.5 ± 7.2**	69.5 ± 6.3	**<0.004***
36 h	**74.6 ± 6**	70.3 ±6.1	**<0.001***

* = significant

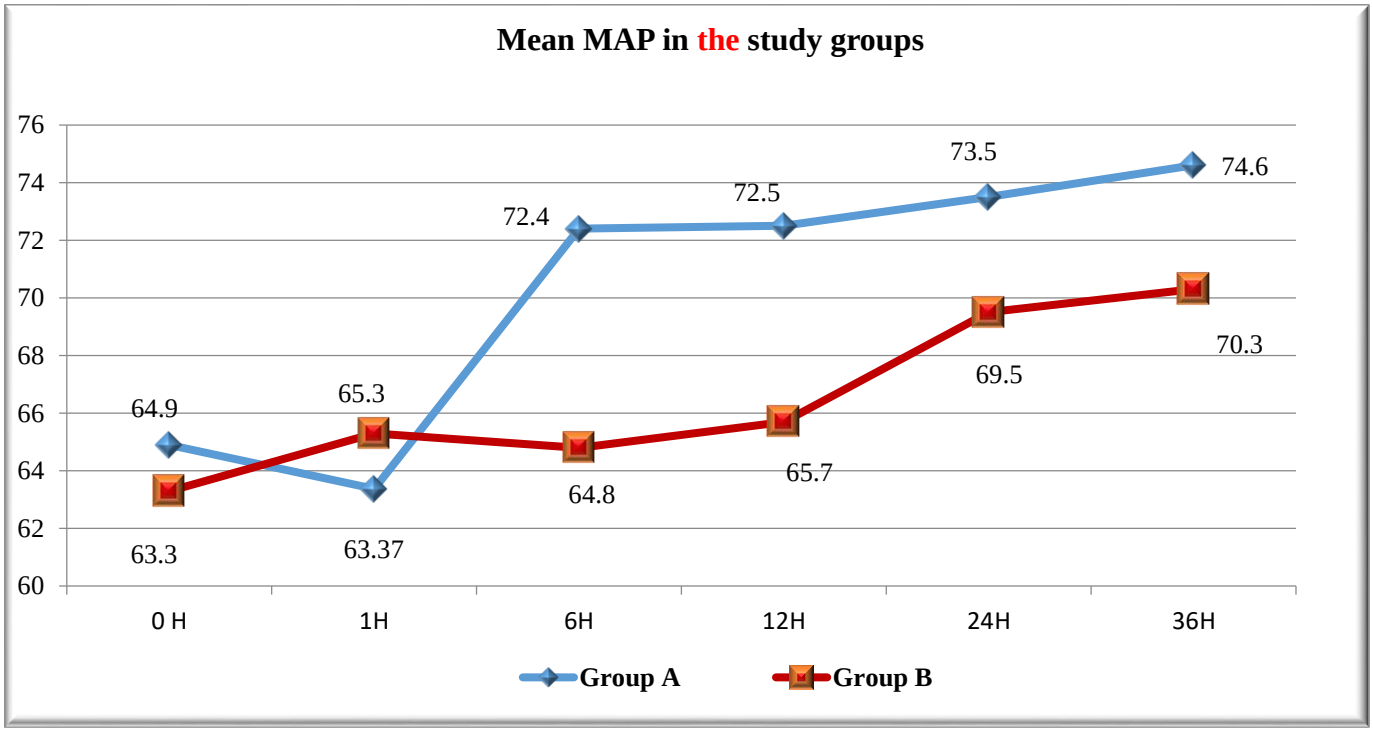

Figure (2): Mean MAP in the study groups

Group A: levosimendan group, group B: Control group

3) Central venous pressure:

Regarding central venous pressure, there was a statistical significant low mean of CVP measures in levosimedan group at zero, 1, 6, 24, and 36 hours versus control group with no difference at 12 hours (Table 8).

Table (8): Comparison of postoperative measured CVP between both groups at various time intervals

CVP	Levosimendan Group (n=50)	Control group (n=50)	p-value
0 h	**5.5 ± 2.1**	7.2 ± 1.98	**<0.001***
1 h	**5.4 ± 2.3**	7.2 ± 1.9	**<0.001***
6 h	**6.2 ± 1.95**	7.1 ± 1.8	**0.02***
12 h	6.6 ± 1.9	7.1 ± 1.83	0.18
24 h	**5.1 ± 1.61**	6.6 ± 1.97	**<0.001***
36 h	**4.93 ± 1.7**	6.27 ± 1.4	**<0.001***

* = significant

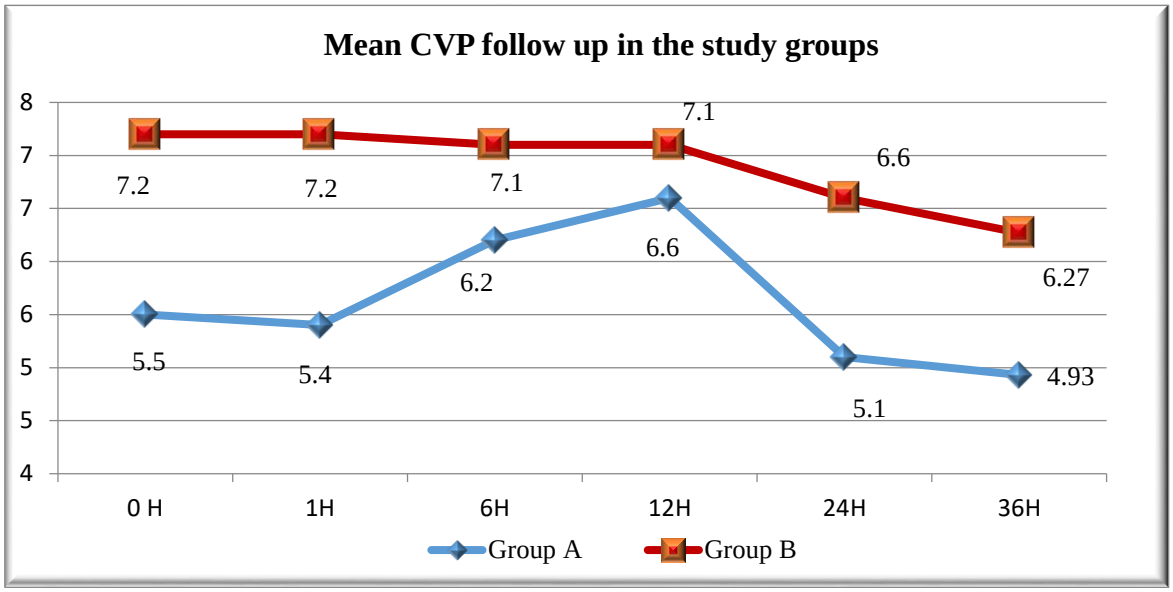

Figure (3): Mean CVP follows up in the study groups
Group A: levosimendan group, group B: Control group

Follow up echocardiography after one week:

The table illustrated that there was a statistically significant difference between study groups as regard postoperative measures of LVED, LVES, PAP (with lower mean among levosimendan group) and EF echocardiography with higher mean among levosimendan group (Table 9).

Table (9): Mean pre- and postoperative echocardiography follow up in different study groups

Variables	Levosimendan Group (n=50)	Control group (n=50)	p-value
PAP			
Preoperative	67 ±9.6	66 ±15.07	0.69
Postoperative	**51.7 ± 6.4**	57.9 ± 8.6	**<0.001***
EF			
Preoperative	38.7 ± 6.5	38.8 ± 6.7	0.94
Postoperative	**37.1 ± 9.3**	33.4 ± 7.1	**0.03***

DISCUSSION

Our study was designed to evaluate the effect of using levosimendan in patients with high risk mitral valve disease undergoing mitral valve surgery in a comparison with a control group regarding postoperative prognosis, hemodynamics, morbidity and mortality. It is a prospective randomized clinical study including two groups of patients. 100 patients with mitral valve disease underwent high risk mitral valve replacement were divided into 2 groups: levosimendan group (50 patients) and control group (50 patients), 59 patients were females (59%) among both groups. While in **Gandham *et al.*** [9] study, 60 patients underwent mitral valve repair / replacement for severe mitral stenosis divided into 2 equal groups (30 patients each), 26 patients were males (44%) while 34 patients were females (56%). In **Ersoy *et al.*** [10] 20 patients with high risk valve surgery divided into 2 equal groups (10 each), 8 patients were males (40%) and 12 patients were females (60%). **Khaled *et al.*** [11] included 60 patients with poor LV punction were divided into 2 groups (30 patient each).

The mean age of the studied patients was 39 ± 13.5 years in group A and 42 ± 9.87 years in group B which is similar to **Gandham *et al.*** [9] who reported mean age of 36.13 ± 7.11 years, Also **Ersoy *et al.*** [10] reported mean age of 49.6 ± 10.7 (levosimendan group), 45.7 ± 7.9 (control group) with p value=0.125 while the mean age of **De Hert *et al.*** [12] **and Sorsa *et al.*** [13] was much higher; 69±10 and 65 respectively. 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 and early rheumatic valve affection in our community.

Our study considered only patients undergoing high risk mitral valve while other types of cardiac surgery were not included. The same was in **Gandham *et al.*** [9] while in **Ersoy *et al.*** [10] any high-risk valve surgery was included. On the other hand, **Khaled M *et al.*** [11]**, De Hert *et al.*** [12]**, Sorsa *et al.*** [13] **and Brezina *et al.*** [14] included any type of cardiac surgeries in patient with left ventricular dysfunction.

As regards timing to start levosemindan, it was started after cardiac surgery or during CPB weaning. In only a few studies, levosimendan was started before CPB [15]. **Gandham *et al.*** [9] 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, levosimendan and dobutamine were administered once patient was

rewarmed to 34°C and aortic clamp was released. **Ersoy *et al.*** [10] administered levosimendan just after the induction of anesthesia as a prophylactic measure in patients with high risk valve surgery. **Khaled *et al's.*** [11] patients in study group received levosimendan additionally during CPB weaning at a loading dose of 6-12 mic/kg according to mean arterial pressure over 0.5 hour followed by 24 hours infusion at 0.05 to 0.2 mic/kg/min. **De Hert *et al.*** [12] (compared levosimendan with milrinone in the patients with LVEF of less than 30%) used levosimendan without loading dose and started immediately after aortic cross-clamp release in fixed combination with dobutamine. **Leppikangas *et al.*** [17] administered levosimendan to patients who underwent combined aortic valve and coronary bypass surgery for 24 hours before surgery. They found that both cardiac index (CI) and stroke volume were higher in the levosimendan group and concluded that in patients undergoing risky cardiac surgery, levosimendan improved hemodynamics compared with placebo.

Brezina *et al.* [14] showed that levosimendan infusion after the induction of general anesthesia in high-risk cardiac surgery patients resulted in better outcomes during length of hospital stay and 30-day mortality rate, compared with patients receiving dobutamine and milrinone. In another study by **Tritapepe *et al.*** [18] intravenous bolus administration of levosimendan over a 10-minute period before initiation of bypass resulted in less myocardial injury, a reduction in tracheal intubation time, less requirement for inotropic support and a shorter length of intensive care unit stay, compared with placebo. On the other hand, **Toller *et al.*** [19] 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 yields better results. So levosimendan should not be used as a last resort, and its administration should not be delayed in high risk patients.

In our study, levosimendan was started as infusion at a dose of 0.1 mcg/kg/min immediately after the induction of anesthesia and before CPB. The aim was to improve myocardial performance during CPB weaning, and for myocardial preconditioning effect.

Also, no statistically significant difference was found between our 2 study groups regarding the cardiopulmonary bypass time and the aortic clamp time, which is nearly the same as **Gandham *et al.*** [9], **Ersoy *et al.*** [10] and **Brezina *et al.*** [14]. On the other hand, **Abd Elrahman *et al.*** [20] who conducted a study including 60 patients evaluating the effect of the perioperative use of levosimendan in patients with left ventricular systolic dysfunction undergoing cardiac surgery on cardiopulmonary bypass, they found that the use of levosimendan pre and early postoperatively was associated with facilitated weaning from CPB. Total bypass time in levosimendan group was significantly shorter (65.5±51.0) in comparison with control group (98.0±55.0) (P= 0.03).

There was no significant difference regarding need for pharmacological inotropes between the 2 groups except for noradrenaline, which was more significant in levosimendan group (19 vs. 35), which can be explained by vasodilating effect of levosimendan. This is similar to **Ersoy *et al.*** [10] (5 vs. 2 p =0.160) **and Tritapepe *et al.*** [16] who found no significant difference between both groups. In contrast, **Gandham *et al.*** [9] showed significant need of inotropes administration in levosimendan group (Adrenaline 7 (23.3%) vs. 2 (6.6%), Noradrenaline 14 (46.6%) vs.2 (6.6%), Group inotrope 6 (30%) vs. 26 (86.6%). While **Brezina *et al.*** [14] added dobutamine (low dose of 5 μg/kg/min) to levosimendan in 50% patients in the study group to increase cardiac performance and added milrinone in all patients in control group. But there was no statistically significant difference in the number of patients who needed noradrenaline to maintain sufficient MAP between the groups, which indicates that the degree of vasodilation induced by levosimendan is similar to that induced by dobutamine with milrinone.

Also there was no significant difference in the duration of mechanical ventilation between the 2 groups (6.37 ±2.6 vs. 7.1 ±2.3), a finding concordant with almost all the aforementioned similar studies.

In this study heart rate showed significant difference being higher in the conventional group at mostly all times postoperatively. It can be explained by the fact that using of recommended doses of levosimendan in patients with normal or reduced ejection fraction rarely produces positive chronotropy exceeding more than 10% from baseline, while other inotropes are usually associated with increased myocardial oxygen consumption and heart rate [21]. This went side by side with **Gandham *et al.*** [9] who showed that there was significant difference in heart rate being higher in the conventional group at mostly all times postoperatively. This difference may be because they were mainly comparing dobutamine with levosimendan. In contrast**, Khaled *et al.*** [11] showed no significant statistical difference at all times postoperatively between both groups. Also, **De Hert *et al.*** [12] and **Malliotakis *et al.*** [22] found no statistically significant difference in the heart rate at all times postoperatively between both groups.

In our study mean arterial pressure was statistically significant at 6, 12, 24, 36 hours postoperatively, being higher in the levosimendan group. **Abd Elrahman *et al.*** [20] found also that mean arterial pressure was significantly higher at 24 hours postoperatively in the levosimendan group. On contrary, **Gandham *et al.*** [9], **Khaled *et al.*** [11]**, Malliotakis *et al.*** [22] **and Alvarez *et al.*** [23]**,** showed significantly higher mean arterial pressure but in the conventional group. This may be due to systemic and pulmonary vasodilator effect of levosimendan, leading

to a reduction in blood pressure. While in our study, the vasodilating effect of levosimendan was balanced by adding noradrenaline.

In our study, central venous pressure in almost all times (except at 12 hours) postoperatively was significantly lower in the levosimendan group. Our results agree with **Alvarez *et al.*** [23] who found significantly lower central venous pressure at 6, 12, 24, 48 hours postoperatively with levosimendan administration. **Gandham *et al.*** [9] **and Malliotakis *et al.*** [22] found similar results. This can be explained by the reduction in systemic and pulmonary vascular resistance caused by levosimendan. On the other hand, **Khaled M *et al.*** [11] found significantly lower central venous pressure 6 h, 12 h postoperatively in the conventional group. This disagreement may be explained because there was no fixed IV fluid protocol in our study and their studies. That was one of our study limitations.

Regarding duration of ICU stay, we found no significant difference between the 2 groups, a finding that's similar to **Gandham *et al.*** [9], **Ersoy *et al.*** [10] and **Brezina *et al.*** [14].

In our study there was a significant difference in left ventricular function (EF%) (37.1 ± 9.3 vs. 33.4 ± 7.1) and pulmonary artery pressure (51.7 ± 6.4 vs. 57.9 ± 8.6) between the 2 groups postoperatively determined by echocardiography. Supporting our results, **Khaled *et al.*** [11] found that using levosimendan achieved statistically significant improvement in left ventricular function (EF%) postoperatively compared to conventional group and (36.90 ± 4.53 VS 33.73 ± 2.96). Also **Ersoy *et al.*** [10] did serial measurement of cardiac output (CO), CI, and mean PAP postoperatively for each patient using a thermodilution catheter and showed marked decrease in the pulmonary arterial pressure and increase in CO and CI was observed in the levosimendan group, but the changes in the control group was not significant. So early use of levosimendan was associated with greater preservation of cardiac function after CPB and a significant improvement in PAP due to its vasodilating effect that would result in a better recovery of patients. On the other hand, **Gandham *et al.*** [9] showed no significant difference in LVEF and PAP postoperatively between 2 groups.

In our study, mortality was higher in the conventional group compared to levosimendan group but that difference wasn't statistically significant (3 vs. 5). That's similar to **DeHert *et al.*** [12] who showed a non-significant effect on mortality (p = 0.224), and **Khaled *et al.*** [11] (10 patients vs. 9 patients) with (p = 0.781). Similarly, **Mehta *et al.*** [24] in the mega trial LEVO-CTS had found that levosimendan did not affect the primary outcome (mortality) (p = 0.45). Contrarily, **Brezina *et al.*** [14] documented 30-day mortality significantly lower in the levosimendan group (0% versus 41.7%; P=0.04). This large difference was explained by the small number of patients in this study (10 vs 12). Other similar studies as **Gandham *et al.*** [9], **Malliotakis *et al.*** [22] **and Alvarez *et al.*** [23] were focusing mainly on the hemodynamic effect of levosimendan, and didn't compare mortality of both groups.

Limitations:

We want to draw the reader attention to some limitations of this study. Some confounding factors were present, for example the mode and parameters of mechanical ventilation were left to the consultant of every day to judge, there was no fixed fluid protocol and fluid therapy was managed per the preference of the on duty ICU consultant. Lack of invasive cardiac function monitoring (cardiac index, stroke volume index, systemic and pulmonary vascular resistance) caused by the paucity of the resources. Longer follow up with echo evaluation 30 and 90 days postoperatively might give more insights regarding the actual benefit of adding levosimendan to the conventional management of high risk mitral valve surgery patients.

CONCLUSION

Early use of levosimendan in high risk mitral valve replacement patients improves hemodynamics, making it a useful choice to prevent postoperative LV dysfunction in this patient population.

Conflict of interest: The authors declare no conflict of interest.
Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Author contribution: Authors contributed equally in the study.

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