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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 Natinaol 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 how ever 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*

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I. 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 course[(1)].

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 LCOS[(2)].

Also peri-operative myocardial dysfunction is associated with organ failure, prolonged intensive-care stay, delayed recovery and prolonged hospital admissions[(3)].

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 inflammation[(4)].

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 cardiotoxic[(5)].

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.

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 triplemechanism of actionthat provides positive inotropy with a neutral effect on oxygen consumption, and with preconditioning, cardioprotective, anti-stunningand anti-ischemic effects[7].

In a recent meta-analysis of clinical trials, Mehtaand colleagues evaluated the effects of levosimendan in cardiac surgery patients with and without preoperative systolic dysfunction[1].

Aim of the Work

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

II. Patients and Methods

Studyobjectives

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

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

Study sites and patient population.

This study wascarried out in(Cardiothoracic Department Natinaol 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.

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/min for the first hour and then reduced to 0.1 μg kg/ 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 byechocardiogram, nuclear scan, or magnetic resonance imaging measured at any time within30 d before surgery

Main exclusion criteria:

• Restrictive or obstructive cardiomyopathy, constrictive pericarditis,restrictive pericarditis, pericardial tamponade, or other conditions inwhich 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 venovenoushemofiltration, hemodialysis, ultrafiltration, or peritonealdialysis within 30 d of CABG/mitral valve surgery)
• Estimated glomerular filtration rate 30 mL/min per 1.73 m2 before CABG/valve surgery
• Weight ≥150 kg

• Patients whose systolic blood pressure (SBP) cannot be managed toensure SBP 90 mmHg at initiation of study drug
• Heart rate ≥120 beats/min, persistent for at least 10 min atscreening 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 aortal 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 plannedstart of study drug
• Received an experimental drug or used an experimental medicaldevice 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 hoursbefore surgery, and at, 24, and 48 hours, and day 3,4and 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-brunch block.

2) Post operative renal impairment andreplacement 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) ICUlength of stay.
6) Seconadry inotropic use more than 24 h.
7) 30 days safty 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

Variable	**Levosimendan (n=30)**	**Control (n=30)**	**P-value***
Gender (M/F)	15/15	14/16	1.0#
Age (years)	50.9 ± 14.6	49.3 ± 12.4	0.648
BMI (kg/m^2)	31.6 ± 4.9	34.9 ± 12.0	0.168

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 14male 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

	Levosimendan (n=30)		Control (n=30)		
Variable	Mean	SD	Mean	SD	P-value*
HR (bpm)	97.0	16.3	102.0	11.0	0.173
MAP (mmHg)	74.4	16.3	63.7	13.0	**0.006**
CVP (cmH_2O)	12.8	3.8	13.1	2.3	0.744
Serum lactate (mmol/l)	4.3	3.9	8.8	3.0	**<0.001**
SvO_2 (%)	59.8	8.7	50.4	7.7	**<0.001**
CO_2 gap (mmHg)	5.2	2.3	5.6	2.7	**0.032**
SV (ml)	64.7	12.1	55.7	12.1	0.05
CO (l/min)	5.2	1.4	4.5	0.8	**0.009**
EF (%)	35.1	8.8	26	9.1	**0.044**

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 comtrol 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 levosindan group was (5.2+-1.4) lower than control group (5.6+-2.7)(p value =0.032).
The stroke volume and cardiac out 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

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

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

		Levosimendan (n=30)		Control (n=30)		
Variable	**Time**	**Mean**	**SD**	**Mean**	**SD**	**P-value***
Serum creatinine (mg/dl)	*Day 1*	1.6	0.5	1.7	0.4	0.463
	Day 2	1.6	0.8	1.8	0.7	0.314
	Day 3	1.9	1.3	1.9	0.9	0.890
	Day 4	2.0	1.6	2.1	1.4	0.714
	Day 5	1.9	1.9	2.1	1.7	0.603

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

		Levosimendan (n=30)		Control (n=30)		
Variable	**Time**	**Mean**	**SD**	**Mean**	**SD**	**P-value***
CI (l/min/m^2)	*Day 1*	2.6	0.4	2.3	0.5	**0.017**
	Day 2	2.7	0.6	2.5	0.5	0.161
	Day 3	2.8	0.6	2.5	0.6	0.117
	Day 4	2.9	0.7	2.7	0.7	0.327
	Day 5	3.0	0.7	2.8	0.7	0.238

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

		Levosimendan (n=30)		Control (n=30)		
Variable	Time	Mean	SD	Mean	SD	P-value*
Serum lactate (mmol/l)	*Day 1*	6.5	3.4	8.8	3.0	**0.008**
	Day 2	4.3	3.9	6.6	3.3	**0.018**
	Day 3	3.6	3.7	4.8	3.3	0.194
	Day 4	3.1	3.9	4.3	4.4	0.272
	Day 5	3.0	4.1	3.9	4.9	0.438

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

		Levosimendan (n=30)		Control (n=30)		
	Time	**Mean**	**SD**	**Mean**	**SD**	**P-value***
CK (IU/l)	*Day 1*	3094.5	2300.8	4848.4	2604.7	**0.008**
	Day 2	2450.0	2338.6	4491.3	3268.2	**0.007**
	Day 3	2035.4	2545.2	3310.6	3396.3	0.105
	Day 4	1303.1	1896.2	2560.2	3623.0	0.098
	Day 5	1136.1	2196.3	1553.9	2327.9	0.478
CKMB (IU/l)	*Day 1*	163.0	137.4	265.3	140.9	**0.006**
	Day 2	203.8	419.6	188.1	126.9	0.845
	Day 3	94.2	138.7	166.8	151.7	0.058
	Day 4	58.0	100.3	123.8	113.9	**0.021**
	Day 5	48.4	114.5	90.2	105.3	0.147

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

Table (8): Need and duration of life support in 1st 5 days after surgery in both study groups

Variable	Levosimendan (n=30)	Control (n=30)	P-value*
Need for inotropes			
Dobutamine	18 (60.0%)	19 (63.3%)	1.000
Noradrenaline	11 (36.7%)	21 (70.0%)	0.019
Adrenaline	18 (60.0%)	16 (53.3%)	0.792
Milrinone	1 (3.3%)	5 (16.7%)	0.195
Inotrope duration (days)	3.9 ± 2.9	5.4 ± 2.7	**0.048**
Need for VAD			
IABP	6 (20.0%)	6 (20.0%)	1.000
ECMO	1 (3.3%)	3 (10.0%)	0.612
Any typeof VAD	7 (23.3%)	9 (30.0%)	0.492
VAD duration (days)	4.1 ± 0.9	3.1 ± 1.7	0.154
MV duration (days)	2.7 ± 3.6	5.3 ± 6.6	0.063
Need for RRT	7 (23.3%)	8 (26.7%)	1.000
ICU LOS (days)	6.7 ± 3.1	9.1 ± 5.7	0.050

Data are number (n) and percentage (%).
*Fisher's exact test.
This table shows significant difference in the intropic duration during the 1st 5 days of ICU admission levosimendan duration was about (3.9+-2.9) and the control group was (5.4+-2.7) (p value =0.048)
However there was no significant difference regarding needing for pharmacological or mechanical ventticual support as well as the needing for renal replacement therapy and mechical ventilation time and ICU stay

Table (9): Sixty-day survival in both study groups

		Levosimendan (n=30)		Control (n=30)		
Variable		**n**	**%**	**n**	**%**	**P-value***
60-Day survival	Survived	26	86.7%	23	76.7%	0.506
	Died	4	13.3%	7	23.3%	

Data are number (n) and percentage (%).
*Fisher's exact test.
This table shows no significant difference regarding **Sixty-day survival in both study groups.**

IV. Discussion

Ourstudy designed to test the hypothesis thatlevosimendan is effective in improving outcomes ofhigh-risk patients undergoing cardiac surgery with CPB.

High-risk patients were targeted for enrollment because meta-analysis of available studies on levosimendan suggested greater benefits of the drug in this cohort.In our studythe baseline demographic data were almost equal in both study group with**no significant** statistical difference betweenboth groups.

Number of male to femalewas equal in both group, the Body mass Index among levosimendan group mean±SD31.6 ± 4.9 and controlgroupmean±SD34.9 ± 12.0, regarding the age the levosimendan group mean±SD50.9 ± 14.6 and in control group mean±SD 49.3 ± 12.4

It wasconcordant with other international studies like**De Hert *et al.*[(8)]**who conducted a study enrolling30 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±SD26.2±3.7.

Regarding pre operativecomorbidity and past medical history our study also showed**no significant** statistical difference regarding preoperative comorbidities, preoperativemedication, hemodynamics,labs,Echo finding,as well as the NYHA class of both study groupswhich showed almostthe similarly of basic characters 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 withvariationsof typesof 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 withoutdomination of one type over others.

But this isdisconcordantwith **Alvarez *et al.*[(9)]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.*[(8)]**had 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 enrolling12 patients evaluating the Hemodynamic Effects of Levosimendan for Low Cardiac Output After Cardiac Surgery) determinedthat 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 vale 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 oflevosimendan 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 respectivelyofcontrol 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. 60patients received either Levosimendan as a12 mic/kg bolus followed by0.2 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 **Gandham*et al.*[12],**who conducted a study enrolling60 patients evaluating acomparison of hemodynamic effects of levosimendan and dobutamine in patients undergoing mitral valve repair / replacement for severe mitral stenosisfound 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 undergocardiac 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]**whostates that there was no statistically difference in the heart rateat all times postoperative between both groups (p >0.05).

Also, **Malliotakis *et al.*[13]**stated that there was no significant changes in heart rate postoperative (p>0.05).

In contrast,**Gandham*et al.*[12]**showed there was significance difference in heart rate being higher in the conventionalgroupat 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 controlgroup.

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 hrshrs postoperative were statistically notsignificantbetween both groups being lower in the levosimendan group.

Our resultsdisconcordance 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.*[13]determined that there was significant difference in central venous pressure at 6,12,24hrs postoperative from baseline levosimendan infusion p<0.05.

Gandham*et 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 withour study.

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

In concordance with other studies**Alvarez *et al.*[9]**showed thatsignificant difference in mixed venous oxygen saturation at 6, 12, 24, 48hrs postoperative between both groups with p<0.05.

Malliotakis *et al.*[13]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 **Shah*et al.*[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 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.*[1]** (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 ventricular assist device. However, there werefewer 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)**[1].**

In addition, the levosimendan-treated patients experienced statisticallysignificantly 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**Lomivorotov*et al*.[15]** 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; I2 = 75%; for heterogeneity = 0.003, with 1438 patients included and 6 RCTs).

Additionally,**Levin*et al.*[16],** showed that the preoperative use of levosimendan started 24h before surgery, with a loading dose of 10mic/g/kg infusion for 1h that was followed by continuous infusion of 0.1micg /kg /min infusion for 23h Levosimendan result in well maintained hemodynamic andreduce 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.*[17],** 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 outcomeHowever, 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 increasepostoperative ejection fraction than the postoperative ejection fraction with the preoperative, intra operative andearly postoperativeuse of levosimendan p=0.001

In concordance to our results, **Ersoy*et al.*[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-levosimendangroup (G4))evaluating the effect ofPreoperative 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.*[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,**Leppikangas *et al.*[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 the4-day postoperative period(P < 0.05). LVEF maintained in the levosimendan group while the control group showed a decrease LVEF).

Similarly, **Reynolds*et al.*[20],** who conducted a Prospective randomized double-blind/vs. placebo on 24 cardiac surgicalpatients evaluating the effect ofLevosimendan 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, **Barisin*et al.*[21],** who conducted a study on 24 cardiac surgerypatients 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 for15min 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=0.018each).The stroke volume index was significantly higher for levosimendan at 10min (P=0.018),but not at 60 min(p= 0.063).

In addition, **S. Barisin*et al.*[(21)],**had found a Significant increases 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 significant increased stroke volume and decreased systemic vascular resistance.

Sixty-day survival in both study group

In our study, **mortality incidence** with use of levosimendan was lowerthan mortality withcontrol 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 disconcordance with our work, **Levin*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 24h before surgery, with a loading dose of 10micg/kg infusion for 1h that was followed by continuous infusion of 0.1micg /kg /mininfusion for 23h.Overall, 252patients participated in the study. Levosimendan reduced mortality compared to placebo (3.9%vs.12.8%;P value= 0.05).

In concordance**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 large number of study population 880 patients in**Mehta*et al.*[(1)]**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 studywill 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, recomended 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.

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