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The effect of histidine-tryptophan-ketoglutarate cardioplegia alone or combined with preoperative infusion of levosimendan on vasoactive inotropic score in patients with poor cardiac function undergoing coronary artery bypass grafting

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ABSTRACT

Background: Patients with poor left ventricular function undergoing cardiac surgery frequently require inotropic drug support immediately after cardiopulmonary bypass. Levosimendan is an effective agent that acts via two complementary mechanisms. It enhances cardiac contractility and reduces cardiac workload. Aim: to assess the effect of histidine-tryptophan-ketoglutarate cardioplegia (HTK cardioplegia) alone or combined with preoperative infusion of levosimendan on the vasoactive inotropic score in patients with poor left ventricular function undergoing coronary artery bypass grafting. Material and method: this double-blinded randomized controlled trial was carried on 100 patients, divided into two groups; Levosimendan group ($n = 49$): patients received 0.1ug/kg/min levosimendan without loading, 12 hours preoperatively and continued for a total of 24 hours. Control group ($n = 51$): patients received a placebo 12 hours before surgery and continued for a total 24 hours. Both groups received HTK cardioplegia after cross-clamping of the aorta approximately 20 ml/kg into the ascending aorta over 6–8 minutes at a temperature of 4–10°C. Results: Levosimendan group was superior to control group with statistical significance regarding the need of intraaortic balloon pump (IABP), vasoactive inotropic score over the first 24 hours, troponin levels over the first 72 hours, ICU stays, hospital stay, and cumulative hospital costs. Although the incidence of postoperative low Cardiac output syndrome (LCOS), atrial fibrillation (AF), acute kidney injury (AKI), and overall mortality was lower in levosimendan group, but all were not statistically significant. Conclusion: Preoperative infusion of levosimendan combined with HTK cardioplegia in patients with poor cardiac function decreased vasoactive inotropic score and lowered the costs of hospital stay.

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Levosimendan; HTK; Custodiol; CABG; preconditioning

1. Background

Low preoperative left ventricular function is common in patients undergoing cardiac surgery, especially those scheduled for coronary artery bypass graft (CABG) surgery. The management of patients with moderate or severe left ventricular dysfunction undergoing cardiac surgery remains challenging [1].

Numerous perioperative factors have been put forth as mortality predictors and used in routine clinical practice to identify individuals who are more vulnerable. The best indicator for poor outcome is low ejection fraction (EF). In fact, the necessity for inotropic support and postoperative low cardiac output syndrome (LCOS) which is caused by an inadequate cardiac pump function includes a decrease in the cardiac output index (CI) to <2.2 L/min/m^2 and a systolic blood pressure of <90 mmHg, in conjunction with signs of tissue hypoperfusion (cold periphery, clammy skin, oliguria, elevated lactate level) in the absence of hypovolemia, are linked to poor LVEF [2].

Variable degrees of myocardial stunning and/or myocardial injury resulting from ischemia during aortic cross-clamping further worsen preexisting poor ventricular performance, and inotropic treatment during cardiopulmonary bypass (CPB) is often necessary. Presently available inotropic drugs improve myocardial contractility by raising the concentration of cyclic adenosine monophosphate, which in turn raises the calcium concentrations in the heart. In patients with prior ventricular dysfunction, this effect is linked to an increase in myocardial oxygen demand, which may further modify the already disturbed myocardial oxygen balance [3].

Levosimendan is a potent agent that functions through two interdependent mechanisms, by enhancing myofilament response to intracellular calcium, it

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improves cardiac contractility [4]. It reduces the cardiac workload by opening the K_{ATP} channels for the dilation of blood vessels. The pharmacokinetics of levosimendan are linear at the therapeutic dose range of 0.05–0.2 mcg/kg/min.It has a short half life (about 1 hour) after intravenous infusion that enables fast onset of action of the drug and steady state is reached within 5 h after continuous infusion initiation [5]. Levosimendan had been recognized as having a long-acting metabolite (OR-1896) with a half-life of 80 hours. Accordingly, the pharmacologic effects of this metabolite may persist for approximately 1 week. Positive inotropic, anti-stunning, anti-ischemic, and vasodilator effects have been shown in humans when levosimendan is administered to patients suffering from acute myocardial infarction [6].

2. Aim of the study

To assess the effect of HTK cardioplegia alone or combined with preoperative infusion of levosimendan on the vasoactive inotropic score in patients with poor left ventricular function undergoing coronary artery bypass grafting.

3. Methodology

The protocol of this study is registered in the Pan African Trial Registry (www.pactr.org) database ID No. (PACTR202207785952318) after obtaining the approval of the Faculty of Medicine, Ethics Committee of Ain Shams University, approval number (FMASU MD142/2022).

Inclusion Criteria: Patients of both sexs aged 40–70 year with poor cardiac function < 40%, NYHA class ll, lll undergoing isolated elective CABG, Cross clamp time <120 minutes.

Exclusion Criteria: severe renal or hepatic disease, severe mitral regurgitation, redo operation, complex cardiac surgery, neurological deficits, or patient refusal.

4. Randomization and group allocation

Patients were randomly assigned in a double-blinded fashion, randomization by a computer-based program after approval to be enrolled in the study during the preoperative visit.

By using PASS 11 for sample size calculation, setting power at 80%, alpha error at 5% and after reviewing previous study results showed that the mean vasoactive inotropic score among patients who underwent coronary bypass and took levosimendan was lower than that placebo (22.79 ± 9.38 versus 35.39 ± 7.61, respectively); based on that, a sample size of at least 18 patients undergoing coronary bypass will be sufficient to achieve the study objective. We included 102 patients divided randomly into two groups (51 patients in each group) to increase power of the study and for further analysis of different outcomes [7].

Levosimendan group (*n* = 49): patients received 0.1 ug/kg/min levosimendan without loading,12 hours preoperative at a rate of 2 ml/hr and continued for a total of 24 hours.

Control group (*n* = 51): patients received a placebo,12 hours preoperative at a rate of 2 ml/hr and continued for 24 hours.

Both group's syringes were prepared and wrapped with an aluminum foil to ensure blinding and levosimendan is a photosensitive drug. Both groups received HTK cardioplegia after cross-clamping of the aorta approximately 20 ml/kg into the ascending aorta over 6–8 minutes at a temperature of 4–10°C (See Figure 1).

5. Study procedure

Patients were admitted to the intermediate care unit,12 hours preoperative. Central venous line and arterial line were inserted under local anesthesia and sedation. Five leads ECG, pulse oximetry and invasive blood pressure were applied. Levosimendan infusion was prepared by by Diluting a vial 12.5 mg (5 mL) in 250 mL glucose 5% [8]. Patients received 0.1 ug/kg/min of levosimendan as continuous infusion 12 hours before surgery at a rate of 2 ml/hr. If blood pressure became below 100/60 mmHg, noradrenaline infusion was started.The control group received placebo (Normal saline 0.9% 50 ml + vitamin B complex "Becozyme®") at a rate of 2 ml/hr. All infusion syringes were covered with aluminium foil as levosimendan is photosensitive.

Patients were premedicated with 0.05–0.1 mg/kg of midazolam intravenously, upon arrival to OR. Standard anesthesia technique was conducted for all the patients according to the anesthesia protocol of Ain Shams University hospital. Monitoring included five leads electrocardiography (ECG), pulse oximetry, invasive blood pressure (IBP), and transesophageal echo (TEE). Anesthesia was induced with fentanyl 3–4 mcg/kg, propofol 1–2 mg/kg, and muscle relaxation was obtained with 0.15 mg/kg cisatracurium. Anesthesia was maintained with sevoflurane 1–2%, fentanyl infusion 1–2 mcg/kg/hr, and cisatracurium 1–3 mcg/kg/min as continuous infusion throughout the procedure.

Before initiation of CPB, patients received heparin 4–5 mg/kg to bring activated clotting time (ACT) >400 sec. A cold crystalloid cardioplegic solution (Custadiol; HTK-Brettschneider solution for cardioplegia, Franz Köhler Chemie GMBH, Alsbach-Hähnlein, Germany) was injected at a dose of 20 ml/kg initially by pressure of 200 mmHg until cardiac arrest over a period of 6–8 minutes after CBP was established and the aorta was cross-clamped. Both groups experienced mild hypothermia (32°C).

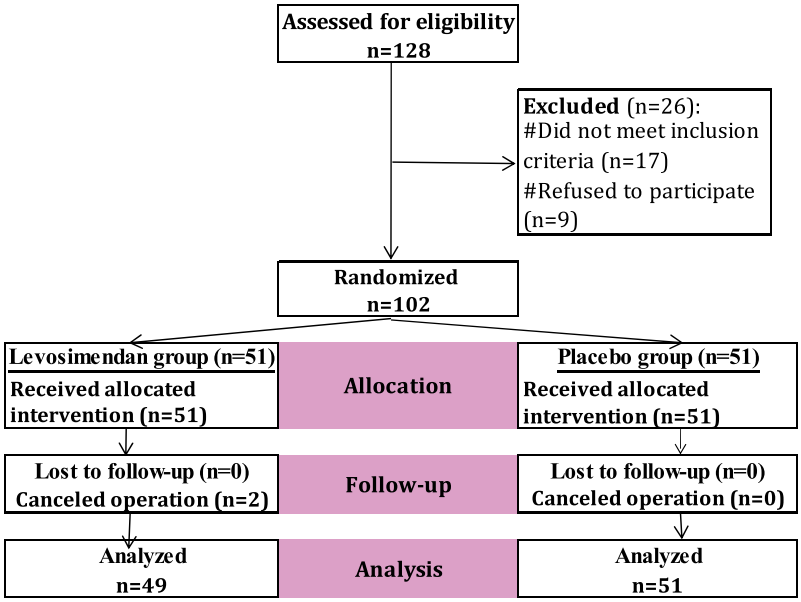

Figure 1. Consort flowchart demonstrating patient allocation.

Weaning of CPB was achieved after ensuring core temperature > 36.5°C, PH > 7.3, hematocrit > 25%, potassium levels between 3.8 and 5mEq and good Cardiac output (cardiac index >2 L/min/m2) as assessed by TEE Hemodynamic targets to be achieved; Heart rate 70–100 bpm, mean arterial pressure (MAP) 70–90 mmHg. If cardiac index (CI) < 2 L/min/m [2] adrenaline infusion was titrated toward the target MAP.Other inotropes can be added as dobutamine or milrinone. If MAP was low (<70 mmHg) and TEE proved fair COP with low systemic vascular resistance (SVR) after preload optimization (vasoplegic syndrome), noradrenaline infusion was started and titrated gradually to get MAP >70 mmHg. If there was inability of weaning from CPB despite pharmacological & preload optimization, Intraaortic ballon pump (IABP) was inserted as mechanical circulatory support. After hemodynamic stabilization, Protamine sulphate (Protamine, Leo Pharma, Zaventem, Belgium) was used to neutralize the heparin's action at a dose of 1 mg for every 100 U of heparin administered. Protamine dosage was additionally directed by ACT readings, which were to be 140 seconds or less.

Postoperative, All patients were transferred to the cardiac surgical ICU. The patients were kept sedated and ventilated till stabilization with the following criteria before decision to extubate : systolic blood pressure >90 mmHg, mean blood pressure >60 mmHg on minimal VIS, adequate urine output 0.5–1 ml\Kg\hr, temperature 36.5–37.2°C, no signs of bleeding with drain output (<100 ml/hr) and normal lactate levels, adequate response to verbal commands, spontaneous respiratory efforts on continuous positive airway pressure (CPAP) 5–8 mmHg with a fractional inspired oxygen < 0.4, $PaCO_2$ <50 mmHg and pH > 7.3.

During ICU stay, blood levels of troponin were serially measured upon admission and every 6 hours in day one then daily.

Patients were eligible to be transferred out of ICU when hemodynamically became stable without vasopressors or any inotropic support and minimal chest tubes drainage.

Patients were discharged from hospital whenever the wounds were dry and clean, independent ambulation and feeding and stable hemodynamic and rhythm.

The inotropic score formula was calculated as follows [9]:

Vasoactive-Inotropic Score (VIS) =
Dopamine dose (mcg/kg/min) +
Dobutamine dose (mcg/kg/min) +
100 × Epinephrine dose (mcg/kg/min) +
10 × Milrinone dose (mcg/kg/min) +
10,000 × Vasopressin dose (units/kg/min) +
100 × Norepinephrine dose(mcg/kg/min

6. Statistical package and analysis

Values were presented as mean ± standard deviation for normally distributed data and as median and range for non normally distributed data. Qualitative data was compared by the Chi-square test. Quantitative data were checked for normality by Shapiro-Wilk test. Normally distributed data were compared using the unpaired t-test. Data following other distributions than normal were compared between groups by Mann–Whitney test. All tests were bilateral, and the level of significance was determined at a P-value of < 0.05. Inferential statistics were performed by statistical software IBM-SPSS version 24.

Table 1. Comparison between groups as regard demographic characteristics, comorbidities, and baseline clinical characteristics.

Variables			Levosimendan group ($N = 49$)	Control group ($N = 51$)	p-value
Age (years)			57.0 ± 5.9	55.3 ± 6.8	^0.188
Sex n(%)	Male		34 (69.4%)	35 (68.6%)	#0.935
	Female		15 (30.6%)	16 (31.4%)	
BMI (kg/m^2)			29.7 ± 3.8	29.1 ± 4.2	^0.398
BSA (m^2)			2.1 ± 0.1	2.1 ± 0.2	^0.206
Smoking, n (%)			9 (18.4%)	7 (13.7%)	#0.527
Hypertension, n (%)			23 (46.9%)	20 (39.2%)	#0.435
DM, n (%)			24 (49.0%)	28 (54.9%)	#0.553
COPD, n (%)			12 (24.5%)	10 (19.6%)	#0.556
Previous stroke, n (%)			4 (8.2%)	5 (9.8%)	§0.999
Hemoglobin (gm/dL)			11.9 ± 2.3	11.4 ± 1.8	^0.244
Creatinine (mg/dL)			0.90 ± 0.13	0.92 ± 0.17	^0.658
Ejection fraction (%)			34.4 ± 4.8	34.3 ± 5.4	^0.927
LVEDD (cm)			6.6 ± 0.6	6.8 ± 0.5	^0.236
ASA		III	49 (100.0%)	51 (100.0%)	NA
NYHA		III	49 (100.0%)	51 (100.0%)	NA
EURO			6.2 ± 1.9	6.7 ± 2.7	^0.233

Data are presented as Mean±SD or n (%). BMI: Body mass index. BSA: Body Surface Area. DM: Diabetes Mellitus. COPD: Chronic Obstructive Pulmonary Disease. LVEDD: Left End-Diastolic Diameter ASA: American Society of Anesthesia. NYHA: New York Heart Association. EURO: European Society of Cardiology. NA: Not applicable. ^Independent t-test. #Chi square test. §Fisher's Exact test.

Table 2. Comparison between groups as regard operation characteristics.

Variables		Levosimendan group ($N = 49$)	Control group ($N = 51$)	p-value
Graft vessels	Two	7 (14.3%)	9 (17.6%)	§0.213
	Three	40 (81.6%)	35 (68.7%)	
	Four	2 (4.1%)	7 (13.7%)	
CPB duration (minutes)		182.6 ± 18.0	177.9 ± 13.0	^0.130
Ischemia time (minutes)		120.1 ± 10.3	120.0 ± 10.5	^0.938
VF rhythm, n (%)		19 (38.8%)	21 (41.2%)	#0.806
Intraoperative balloon, n (%)		6 (12.2%)	16 (31.4%)	#0.021*

Data are presented as Mean±SD or n (%). CPB: Cardiopulmonary bypass. ^Independent t-test. #Chi square test. §Fisher's Exact test. *Significant.

7. Results

There was no statistical significant difference between both groups regarding demographic characteristics, comorbidities, and baseline clinical characteristics among the study groups (Table 1).

There was no statistical significant difference between the studied groups regarding operation characteristic except the intraaortic ballon Table 2

Mechanical ventilation time, post operative EF and postoperative stays at intensive care unit and hospital ward were significantly shorter among the levosimendan group. Post-operative atrial fibrillation (POAF), low cardiac output syndrome (LCOS), acute kidney injury (AKI), and mortality were non-significantly less frequent among the levosimendan group (Table 3).

8. Discussion

The current study was conducted on a group of patients undergoing CABG with left ventricular function impairment one group received levosimendan 12 hours preoperatively and continued for 24 hours while the other group received a placebo, vit B6 ampoule "Becozyme®" as it is yellow coloured like levosimendan with infusion rate adjusted to 2 ml/hr.The two groups were comparable as regarding baseline data.

Table 3. Comparison between groups as regard postoperative outcomes and complications.

Lactate day 1 (mmol/l)			
Peak	5.8 ± 2.0	9.1 ± 2.4	^<0.001*
Post operative EF (%)	51.4 ± 3.2.	44.6 ± 4.2.	^<0.001*
Postoperative stay			
Mechanical ventilation (hours)	13.7 ± 6.1	16.6 ± 5.5	^0.015*
Intensive care unit (days)	4.0 ± 1.4	4.9 ± 1.3	^0.001*
Hospital ward (days)	7.9 ± 2.6	9.1 ± 2.5	^0.017*
Complications			
LCOS, n (%)	6 (12.2%)	9 (17.6%)	#0.449
AKI, n (%)	4 (8.2%)	11 (21.6%)	#0.061
Mortality, n (%)	4 (8.2%)	9 (17.6%)	#0.159

^Independent t-test. #Chi square test. *Significant.

Levosimendan had favorable outcomes superior from all aspects: lower VIS at 0, 24, 48 hours, the lower need for IABP, lower postoperative troponin at different time intervals, lower peak lactate during postoperative day one than the control group with shorter ICU and hospital stays, less incidence of low cardiac output syndrome, and result of lower costs spent in patients received levosimendan.

Patients with poor LVEF are more likely to experience stormy postoperative courses with high risks of complications and fatalities [10–12].

The cornerstone of myocardial protection is cardioplegia. HTK cardioplegia was chosen because it supports uninterrupted surgical procedures and is designed to achieve heart protection for up to 4 hours after one dose [13]. In most clinical trials, HTK solution demonstrated advantages at the biochemical level in accelerating the healing and preserving of the myocardium [14], especially with long cross-clamp time with less risk of endothelial injury [15] due to its special characteristics which include: low sodium content, which allows it to induce cardiac arrest during diastole by inhibiting the action potential's rapid phase [16], tryptophan, which helps to keep the cell stable, and ketoglutarate, which is said to encourage the synthesis of ATP during reperfusion [17], mannitol aids in removing pro-oxidants and minimizing cellular edema, and for maintaining the intracellular pH using histidine as a protein buffer rather than bicarbonate [18].

Logistics of cardioprotection is not limited to cardioplegia but it extends to preconditioning with its types: ischemic or pharmacological by sevoflurane, opioids, adenosine, and levosimendan, all pharmacologic preconditioning agents share in being K_{ATP} channel opener on myocyte and mitochondria. All these measures are integrated to minimize myocardial damage after ischemia-reperfusion injury [19].

Calcium sensitizers, for example, levosimendan and Pimobendan, cause a conformational change in the thin filament regulating protein troponin C, increasing the sensitivity of contractile myofilaments to Ca2+ protein. Theoretically, this results in an increase in the strength of contraction without increasing Ca2+ in the cytosol. Other mechanisms have been suggested, such as the inhibition of phosphodiesterase (PDE), the reduction of pro-inflammatory cytokines, and the opening of K_{ATP} [20]. Suggested theories of durable effects of levosimendan are due to pharmacologically active long-lasting metabolite (OR-1855) for up to 80 hours [21].

Maximum benefits of levosimendan can be evident in two situations first if administered preoperatively and in patients with severe left ventricular dysfunction [22,23], which is reflected in the Solveig and Rivera studies, when levosimendan infusion started late just before weaning of bypass there is no difference in cardiac output in aspects of cardiac index and central venous saturation than controls [24,25].

Preoperative use of levosimendan prime myocardial cells improve the function of the LV, the outcome of patients with complex CABG+MVR procedure using levosimendan facilitated successful weaning of patients from CPB, lower need for IABP insertion. The better hemodynamic profile of levosimendan reflected shorter ventilation and ICU time [26].

In meta-analysis, we included 17 studies in patients who had cardiac operation, levosimendan did not affect mortality in high-quality studies, but in subgroup analysis patients with preoperative ventricular systolic dysfunction had reduced mortality in risk reduction by 42% and shorter ICU stay [27].

In a retrospective study by *Lehman et al*., levosimendan had a lower need for intra-aortic balloon insertion in high-risk CABG patients and a lower need for postoperative dialysis but without significant difference in hospital stay or survival [28].

We noted that levosimendan group showed less incidence of LCOS, Consequently showed less incidence of postoperative manifestations of kidney injury (oliguria, anuria, rising serum creatinine and need for postoperative dialysis).

Levin et al. reported that levosimendan had less incidence of low cardiac output syndrome and better cardiac output from aspects of cardiac index and central venous saturation during the first two postoperative days which was reflected in terms of reduced morbidities and mortality in addition to less incidence of fatal and non-fatal ventricular dysrhythmia [29].

Tritapepe and his colleagues conducted two trials on levosimendan before the institution of CPB in elective CABG cases. The first study recorded lower troponin I in the levosimendan group [30,31]. The second study reported shorter hospital stay, lower inotropic scores and less need for mechanical support in the levosimendan arm [32].

The lower postoperative troponin I and lactic acid in addition to shorter ICU stay and lower incidence of postoperative atrial fibrillation after elective CABG were also reported with levosimendan in other studies [24,33].

Also, there are many reports regarding the cost-effectiveness of the relatively expensive drug levosimendan especially in this high-risk group of patients [34,35]. In addition to the improvement of bed turnover in the ICU especially in the category of surgery with a long waiting list.

Disparities in preclinical models and the clinical context in the subject of myocardial protection can be simply explained by the single target of most clinical trials, despite the well-known diverse array of mechanisms of cell death during ischemia-reperfusion. According to the idea advanced here,

addressing a single mechanism at a time may be insufficient to create a substantial and robust effect in clinical scenarios where numerous uncontrollable variables commonly coexist [36]. We think this was a limitation of the current study and future clinical trials should investigate integrated approaches for example, comparing different combinations of cardioplegia with and without levosimendan searching for the best outcome in myocardial protection during cardiac surgery as the initiative multimodal cardiac protection studied in ProCCard trial [37]. We hope to carry out the next trial with four arms comparing blood cardioplegia and HTK cardioplegia with or without levosimendan, but it needs to be multicenter with a larger sample size to get the best cost-effective strategy in myocardial protection during cardiac surgery.

9. Conclusion

Preoperative infusion of levosimendan combined with HTK cardioplegia in patients with poor cardiac function decreased vasoactive inotropic score, troponins levels, and hospital cost.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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