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Original Article

Impact of Levosimendan on High Sensitivity Cardiac Troponin-T after Valvular Heart Surgery: A Randomized Clinical Trial

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Abstract

Background: Various measures have been used for maintaining adequate cardiac output after valvular heart surgery. The study aimed to evaluate the impact of levosimendan on high-sensitivity cardiac troponin-T after valvular heart surgery.

Methods: This prospective randomized clinical trial included 400 patients. All patients above 18 years who underwent elective cardiac valvular surgery were randomly classified into two equal groups. Group A (n= 200) included patients who received levosimendan during weaning from cardiopulmonary bypass, and Group B (n= 200) included patients who did not receive levosimendan.

Results: Cardiopulmonary bypass, cross-clamp, reperfusion times, and use of inotropes were insignificant between groups. Troponin levels on days 0, 1, and 2 showed a significant decrease in Group A (P<0.001). Postoperative ejection fraction was significantly higher in Group A (66.10 ± 4.41 vs. 46.60 ± 3.98; P<0.001). Duration of mechanical ventilation (4.70± 1.16 vs. 10.70± 0.82; P< 0.001), intensive care (1.90 ± 0.57 vs. 5.90 ± 1.29; P<0.001), and hospital stay (6.90 ± 1.91 vs. 13.40 ± 3.10; P<0.001) were significantly lower in Group A.

Conclusions: Levosimendan could have cardioprotective effects, resulting in a significant reduction of postoperative high sensitivity cardiac troponin-T release after valvular heart surgery. It could be associated with improved left ventricular ejection fraction, short duration of mechanical ventilation, ICU, and hospital stay.

KEYWORDS

Levosimendan; High Sensitivity Cardiac Troponin T; Valvular Heart Surgery

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Introduction

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are prone to myocardial damage and ischemia. Perioperative myocardial injury leads to variable degrees of myocardial dysfunction, from stunning to severe ischemia and infarction [1, 2]. Severe degrees can cause postoperative low cardiac output syndrome (LCOS), a serious complication occurring in 10% of open-heart surgery patients, with a mortality rate of 17% [3].

Various measures have been used for maintaining adequate cardiac output to ensure adequate perfusion and oxygen delivery to tissues. These measures include positive inotropic support, intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), and ventricular-assist devices. Inotropic support is widely used to improve cardiac output; however, there is a debate regarding using it in cardiac surgery due to the associated risk of increasing oxygen consumption, causing further ischemia and arrhythmias [4]. Calcium sensitizer levosimendan is an inotrope that has been investigated for improving postoperative outcomes and mortality after cardiac surgery [1,

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5]. Levosimendan has a triple mechanism of action by acting on calcium-dependent binding to cardiac troponin-C and opening ATP-dependent K-channels on smooth muscle cells in the vasculature and in cardiac mitochondria, which results in an inodilator effect and increases cardiac contractility without increasing oxygen consumption with preconditioning, cardioprotective, anti-stunning, anti-ischemic effects [6, 7]. Additionally, it could provide a cardioprotective effect in the short and long-term [8].

Cardiomyocytes have contractile apparatus composed of Troponin T and I; both are more sensitive and specific for detecting myocardial necrosis than creatine kinase-MB [9]. In practice, Troponin-T is released into the serum after ischemic injury [10]. Its measurement can detect minor degrees of myocardial necrosis [11].

Typically, after uncomplicated cardiac surgery, there is a noticeable increase in levels of cardiac troponin T [12, 13], which is related to ischemic injury [10, 14].

Therefore, we measured cardiac troponin-T as an indicator of ischemic injury and compared troponin-T levels with and without levosimendan after valvular heart surgery.

Patients and Methods

This prospective randomized clinical trial study included 400 patients recruited from the Cardiothoracic Surgery Department at Tanta University Hospitals and other cardiac surgery centers in a period starting from June 2019 to June 2021. Written informed consent was obtained from the patients before enrollment. The Ethics Committee of the Faculty of Medicine, Tanta University, approved the study (Approval code 33113/05/19).

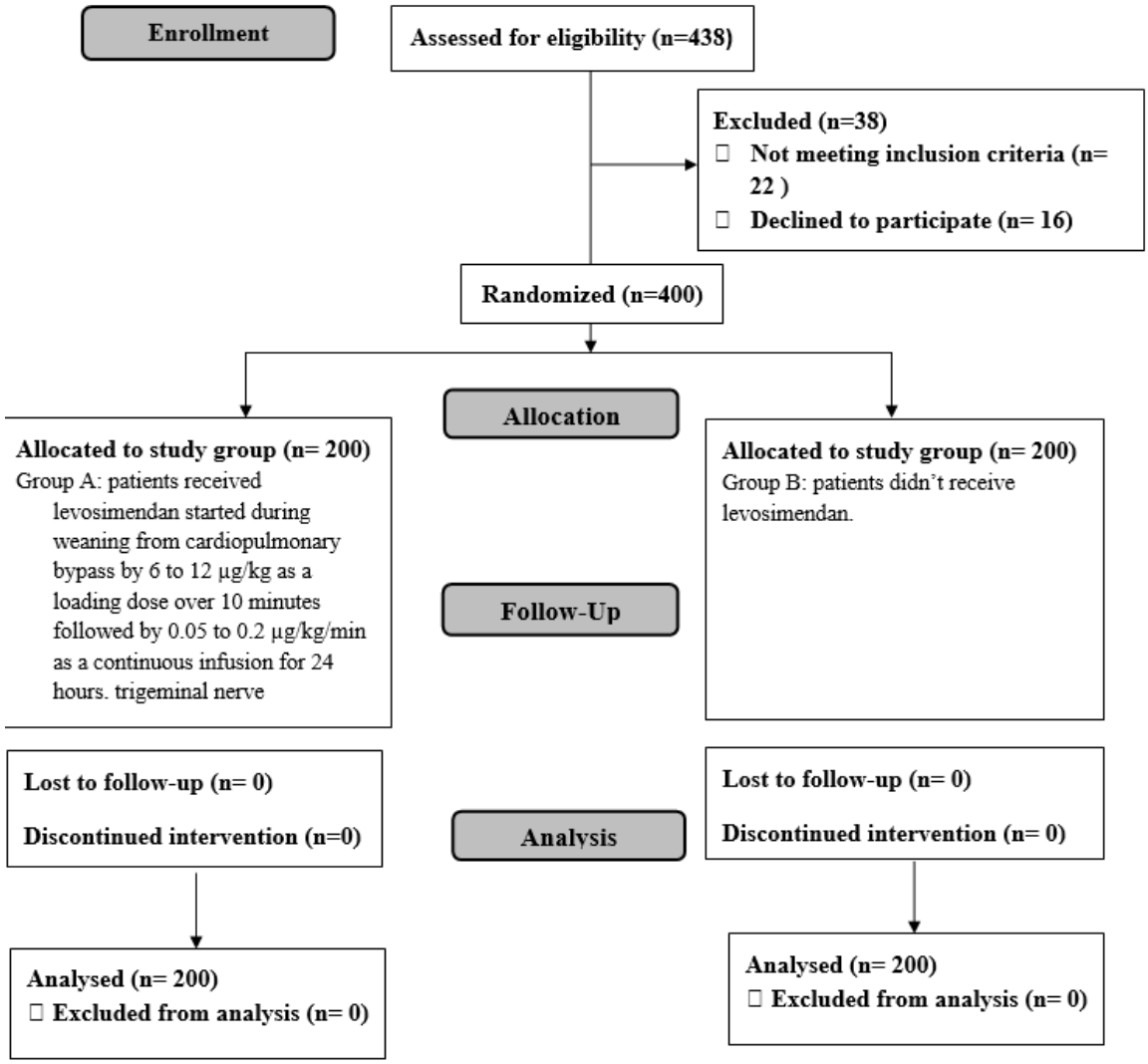

Figure 1: The randomized trial flow diagram, including enrollment, intervention allocation, and analysis

All patients above 18 years, with ejection fraction (EF) >50% undergoing elective cardiac surgery for single or double valve replacement or repair were included. Patients below the age of 18, with EF>50%, significant mechanical obstructions affecting ventricular filling (e.g., atrial myxoma or extracardiac tumor), permanent pacemaker, or implantable cardioverter-defibrillator system were excluded. Additionally, we excluded patients suffering from terminal renal failure or decompensated hepatic failure, or endocarditis.

The primary outcome was high-sensitivity cardiac troponin T. Secondary outcomes were left ventricle ejection fraction, intensive care unit and hospital stay, and In-hospital morbidity and mortality rate.

Randomization

Blocked randomization was used to randomly allocate 400 patients into two equal groups by computer-generated sequence through sealed opaque envelopes. Group A (n= 200) included patients who received levosimendan during weaning from cardiopulmonary bypass in a dose of 6 to 12 µg/kg as a loading dose over 10 minutes followed by 0.05 to 0.2 µg/kg/min as a continuous infusion for 24 hours. Group B (n= 200) included patients who did not receive levosimendan.

If any form of cardiac arrhythmia (e.g., AF) or hemodynamic compromise (MAP ≤ 70 mmHg) occurred, levosimendan infusion was stopped and continued after 2 hours.

All patients in this research were subjected to the following; preoperative baseline entire history and clinical examination, electrocardiography, echocardiography, plain chest x-ray, coronary artery angiography (CAG), laboratory investigations (complete blood count, liver function test, renal function test, coagulation profile, serum electrolytes, arterial blood gases (ABG), erythrocytes sedimentation rate (ESR), C-reactive protein (CRP), random blood sugar (RBS), urine analysis, high sensitivity cardiac Troponin-T level, and dental and otorhinolaryngology consultation for exclusion of any septic focus.

Intraoperative data were total cardiopulmonary bypass, aortic cross-clamp, reperfusion times, and inotropic support.

Postoperatively, all patients' hemodynamics were monitored for the first 48 hours. We collected inotropic support and duration data, electrocardiography, echocardiography, high sensitivity cardiac Troponin-T, duration of mechanical ventilation, intensive care unit, and hospital stay. Troponin-T was evaluated at day zero, first and second day.

Table 1: Patients' associated comorbidities and type of operation of studied groups. Continuous data were presented as mean and standard deviation and categorical data as numbers and percentages

	Group A (n= 200)	Group B (n= 200)	P-value
Comorbidities			
Hypertension	53 (26.50%)	61 (30.50%)	0.27
Diabetes mellitus	19 (9.50%)	31 (15.50%)	0.07
Smoking	44 (22%)	53 (26.50%)	0.29
Renal impairment	23 (11.5%)	36 (18%)	0.07
Atrial fibrillation	118 (59%)	118 (59%)	>0.99
EuroSCORE II	5.3 ± 2.63	5.7 ± 2.72	0.14
Type of operation			
Aortic valve replacement	36 (18%)	36 (18%)	0.07
Double valve replacement	55 (27.50%)	76 (38%)	
Double valve+ tricuspid repair	54 (27%)	41 (20.5%)	
Mitral valve replacement	53 (26.50%)	39 (19.50%)	

Table 2: Bypass time (min), Cross clamp time (min), Reperfusion Time (min), and inotropic use and Troponin T (pg/mL) levels at Preoperative, Day 0, Day 1, and Day 2 in studied groups. Continuous data were presented as mean and standard deviation

	Group A (n = 200)	Group B (n = 200)	P-value
Bypass time (min)	91.00 ± 27.873	94.8 ± 26.1	0.16
Cross-clamp time (min)	84.3 ± 25.956	87.00 ± 7.149	0.16
Reperfusion time (min)	12.6 ± 3.893	13.20 ± 5.613	0.35
Associated inotropes	154 (77%)	137(68.50%)	0.06
Troponin T (pg/mL)			
Preoperative	37.20 ± 14.673	38.70 ± 16.886	0.34
Day 0	297.00 ± 76.891	680.70 ± 84.855	
Day 1	262.40 ± 75.099	569.00 ± 81.302	<0.001
Day 2	166.90 ± 49.190	495.80 ± 84.876	

The sample size calculation:

The sample size calculation was performed using G. power (Universitat Kiel, Germany). According to a previous study [5], the mean length of hospital stay (±SD) in the levosimendan group was 11.1 ± 2.3 versus 12.0 ± 2.5 in the control group based on the following considerations: 0.05 α error and 95% power of the study, effect size 0.374. 13 cases were added to each group to overcome dropout during follow up, therefore 400 cases were recruited.

Statistical analysis:

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25 (IBM Inc., Armonk, NY, USA). Qualitative variables were expressed as mean and standard deviation (SD) and were compared using the unpaired T-test. Categorical variables were expressed as frequency and percentage and were statistically analyzed by the Chi-square test. ANOVA was used for repeated measures analysis. A P-value ≤ 0.05 was considered statistically significant.

Results

In this study, 438 patients were assessed for eligibility, 22 did not meet the criteria, and 16 refused to participate. The remaining 400 patients were randomly allocated into two equal groups (200 patients each). Two hundred patients were followed-up and analyzed statistically. (Figure 1) There were no differences in the preoperative comorbidities and the surgery performed. (Table 1)

Cardiopulmonary bypass, cross-clamp, and reperfusion times and the use of inotropes were insignificantly different between groups. Preoperative troponin showed an insignificant difference between both groups. Troponin T on days 0, 1, and 2 significantly decreased in Group A compared to Group B (P < 0.001) (Table 2). Duration of mechanical ventilation, ICU, and hospital stay was significantly lower in Group A. (P <0.001). Preoperative EF was insignificantly lower in Group B. (P <0.001). (Table 3)

Table 3: Duration of mechanical ventilation (hours), ICU stay (days), hospital stay (days), and postoperative ejection fraction (EF). Continuous data were presented as mean and standard deviation

	Group A (n = 200)	Group B (n = 200)	P value
Duration of MV (hours)	4.70 ± 1.160	10.70 ± 0.823	<0.001
ICU stay (days)	1.90 ± 0.568	5.90 ± 1.287	<0.001
Hospital stay (days)	6.90 ± 1.912	13.40 ± 3.098	<0.001
Preoperative EF (%)	57.8 ± 4.940	58.40 ± 6.818	0.31
EF (%) at day 2	66.10 ± 4.408	46.60 ± 3.978	<0.001

MV: Mechanical ventilation, ICU: Intensive care unit, EF: Ejection fraction

Discussion

There is some degree of global myocardial ischemia and repetitive periods of reperfusion during cardiac surgery with cardiopulmonary bypass, despite the measures to protect the myocardium using cardioplegia, hypothermia, and electromechanical arrest causing myocardial injury in the form of myocardial stunning or hibernation [15].

Myocardial injury releases structural proteins and other intracellular macromolecules into the cardiac interstitium [16], such as cardiac troponin, creatine kinase, and myoglobin. The preferred biomarker for myocardial necrosis is cardiac troponin which has nearly absolute myocardial tissue specificity and high clinical sensitivity [17]. Troponin levels are frequently elevated after cardiac surgery, with the degree of elevation influenced by the nature of the operation. However, troponin levels at 24 hours remain independent predictors of short- and long-term outcomes [18]. Our study used both the clinical outcome and high sensitive cardiac troponin as a biomarker for evaluating the effect of using levosimendan as inotropic support prophylactically among patients undergoing valvular heart surgery with good systolic function.

The use of biomarker high sensitive troponin in detecting myocardial injury was also evaluated by Abd El Wahab and colleagues [19] in their research on the impact of fast cardioplegic arrest induced by adenosine in valvular heart surgery.

We decided to study the beneficial impact of using levosimendan in a prophylactic way as inotropic support in valvular heart surgery. Such inotrope is being used in more than 60 countries and is appreciated by many physicians who showed their interest in using it in patients with heart failure, both in the medical and the surgical fields, owing to the initial studies that showed improvement in hemodynamics and organ function and even suggested reduced mortality [20].

Preconditioning with levosimendan and postoperative usage was an effective strategy in preventing postoperative low cardiac output syndrome in patients undergoing elective coronary artery bypass graft surgery with moderate-severe left ventricular systolic function [21].

In our study, the group of patients that used levosimendan during the weaning of CPB showed a significant reduction in releasing high sensitive troponin compared to the controlled group. A significant difference was also noted in the postoperative course in MV duration, ICU, and hospital stay compared to the controlled group.

Other researchers showed the beneficial effect on myocardial protection, such as Tritapepe and colleagues, [5] who studied levosimendan in patients undergoing coronary artery bypass graft surgery and agreed with our study regarding Troponin release, which was significantly higher in the control group (P = 0.001).

Additionally, Salgado and associates [22] studied 81 patients undergoing coronary artery bypass graft surgery, comparing epinephrine to levosimendan following cardiopulmonary bypass. Their results showed that plasma levels of troponin were lower in the levosimendan group but not in a significant way (P = 0.09). Moreover, they showed that the levosimendan group had a higher postoperative EF with a significant difference compared to the preoperative EF (62% vs. 54%; P= 0.02).

Alberto and investigators [23] performed a meta-analysis to investigate the effects of levosimendan in cardiac surgery and demonstrated that levosimendan has cardioprotective effects, resulting in a significant reduction in postoperative cardiac troponin release, and this went in agreement with us.

In agreement with our clinical outcome regarding the duration of MV, ICU and hospital stay De Hert and associates [24] found that the duration of MV was significantly lower in the levosimendan group compared to the milrinone group in a thirty patient study with low ejection fraction undergoing elective cardiac surgery (P=0.008). This result is also supported by

Kandasamy and colleagues [25], who compared levosimendan and dobutamine on eighty patients with moderate to severe LV dysfunction undergoing off-pump coronary bypass grafting and found that the duration of MV, ICU, and hospital stay were significantly lower in the levosimendan group.

However, the magnitude of the effect of this agent is not as large as previously thought, and some researchers do not strongly recommend routine use in all cardiac surgery settings. Further assessment of the usage of levosimendan requires additional trials [26].

Limitations of the study:

The single-center experience limits the study, and the results need further investigations before generalization. The inclusion of valvular surgery only limits the study, and the results may not apply to other operations.

Conclusion

Levosimendan could have cardioprotective effects, resulting in a significant reduction of postoperative high sensitivity cardiac troponin T release after valvular heart surgery, even in patients with normal preoperative systolic function. Levosimendan could improve the LV ejection fraction and shorten the duration of mechanical ventilation, ICU, and hospital stay.

Conflict of interest: Authors declare no conflict of interest.

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