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Original Article

The Preoperative Use of Levosimendan in Patients undergoing Coronary Artery Bypass Surgery with Low Ejection Fraction

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Abstract

Background: Levosimendan is a calcium sensitizer with positive inotropic, vasodilatory, and cardioprotective actions. Levosimendan infusion time may affect the outcomes. Our objective was to evaluate its efficacy and safety when used before coronary artery bypass grafting (CABG) in patients with low ejection fraction.
Methods: This prospective observational study included 150 CABG patients with ejection fraction ≤ 40% divided into two groups. In the Levosimendan group (n= 75), it was given preoperatively, and in the conventional group (n= 75), myocardial support was used if indicated.
Results: Operative time (344±28.7 vs. 421.4±34.5 min) and cardiopulmonary bypass time (97±17.4 vs. 127.4±24.5) were significantly shorter in the Levosimendan group (P< 0.001, for both). Failure to wean from bypass (13 (17.3%) vs. 23 (30.7%), P=0.06) and the need for intra-aortic balloon pump (6 (8%) vs. 14 (18.7%), P= 0.06) were non significantly lower in the Levosimendan group. The mechanical ventilation duration (12±3.3 vs. 19.6±4.7 h, P= 0.04) and ICU stay (3.8±1.2 vs. 5.3±1.4 days, P < 0.001) were lower with levosimendan. Mortality was non-significantly lower in the Levosimendan group (10 (13.3%) vs. 18 (24%), P= 0.09). There were no differences in atrial and ventricular arrhythmias between groups.
Conclusion: The preoperative use of levosimendan could improve the outcomes in patients undergoing CABG with low ejection fraction. Levosimendan complication profile was comparable to the conventional approach

KEYWORDS
Levosimendan; Low cardiac output; Myocardial ischemia

Introduction

Myocardial stunning and ischemia might occur during cardiac surgery to variable degrees with subsequent myocardial dysfunction. Different methods have been used to reduce myocardial damage during cardiac surgery [1]. Severe myocardial dysfunction can be managed pharmacologically with catecholamines, phosphodiesterase III inhibitors, and calcium-sensitizer (levosimendan), or mechanically with an intra-aortic balloon pump (IABP) or both [2].

Catecholamines are β-1 adrenergic agonists, which increases the cyclic adenosine

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monophosphate (cAMP). Phosphodiesterase inhibitors, such as milrinone, inhibit cAMP degradation and elevate intracellular myocardial calcium levels. On the other hand, levosimendan is a calcium-sensitizing agent that binds to troponin C and makes the myocardial cells more responsive to calcium. This action has an inotropic effect on the cardiac muscle [3].

Moreover, the levosimendan's active metabolites remain in circulation for about one week [4]. Therefore, the levosimendan administration preoperatively could provide more benefits over intraoperative or postoperative use. The preoperative administration allows for the accumulation of levosimendan's metabolites with better hemodynamic support during surgery [5]. However, preoperative use may increase the adverse effects, such as arrhythmia, hypotension, headache, and renal impairment [6]. We aimed to study the efficacy and safety of preoperative use of levosimendan in patients undergoing coronary artery bypass grafting (CABG) with low ejection fraction (EF).

Patients and methods:

Research design:

This study is a prospective observational study that included 150 CABG patients with low EF (≤ 40%). This study was conducted in the cardiothoracic surgery department at Benha University Hospital from March 2017 to October 2020. We allocated patients into two groups. Group A (levosimendan group, n= 75) included patients admitted to the intensive care unit (ICU) 24 hours before surgery and received levosimendan by continuous infusion at a dose of 0.1 µg/kg/min. Group B (conventional group, n= 75) included patients who received levosimendan intraoperative or postoperative when needed.

Inclusion and exclusion criteria:

We included patients with isolated on-pump CABG with no concomitant valve lesions and preoperative EF ≤ 40%. We excluded patients older than 75 or younger than 20 years, patients with chronic chest, liver, or kidney diseases, redo CABG, and patients undergoing other concomitant cardiac surgeries.

Outcomes:

All patients had a thorough preoperative evaluation. Preoperative, intraoperative, and postoperative data, such as the duration of mechanical ventilation, use of inotropes and IABP, ICU and hospital stay, and mortality, were collected. Our primary outcome was the 30-day mortality. The secondary outcomes included intraoperative and postoperative low cardiac output, duration of mechanical ventilation, ICU, and hospital stay.

Statistical analysis

All statistical calculations were done using SPSS statistical program version 23 (IBM Corp, Armonk, NY, USA). Data were described using mean, standard deviation (SD), frequencies, and percentages. A comparison of quantitative variables was done using the Mann-Whitney U test and Chi-square ($\times^2$) or Fisher exact test for qualitative variables. A probability value (P-value) less than 0.05 was considered statistically significant.

Results:

Preoperative data:

There was no significant statistical difference between both groups regarding age, sex, body mass index (BMI), preoperative EF, heart rate and blood pressure, and New York Heart Association (NYHA) dyspnea class. (Table 1)

Operative data:

There was a significant difference between both groups regarding total operative and bypass times. Failure of weaning from cardiopulmonary bypass (CPB) and IABP use were non-significantly higher in Group B. There was no significant statistical difference regarding the cross-clamp time and the number of grafts used (p= 0.45 and 0.99, respectively). (Table 2).

Postoperative data:

There was no statistical difference in arrhythmia between groups. Hypotension was more frequent in the levosimendan group but without significant difference. The need for Inotropic support was significantly higher in Group B (p= 0.02). However, the rate of ICU-IABP use was not significantly different between groups. There

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Table 1: Comparison between the two groups' demographics and clinical parameters. Data were presented as mean and SD or number (%)

	Group A (n=75)	Group B (n=75)	P-value
Age (years)	57.3±10.5	58.4±11.2	0.75
Male	48(64%)	51(68%)	0.39
BMI (kg/m^2)	30.8 ± 5.7	32.3 ± 3.1	0.67
Medical history			
Smoking	41 (54.7%)	45 (60%)	0.26
Diabetes Mellitus	57 (76%)	54 (72%)	0.39
Hypertension	64 (85.3%)	66 (88%)	0.57
Atrial Fibrillation	12 (16%)	9 (12%)	0.4
Heart rate (b/min)	83.6±9.3	84.7±8.3	0.75
Diastolic BP (mmHg)	76.3±12	81.2±13.7	0.17
Systolic BP (mmHg)	122.8±18.7	128.4±20.6	0.12
Ejection fraction (%)	36.5±3.1	35.7± 4.3	0.82
NYHA class			
II	29 (38.7%)	33(44%)	
III	40(53.3%)	36(48%)	0.26
IV	6(8%)	6(8%)	

BMI: body mass index; BP: blood pressure; NYHA: New York Heart Association

was a significant difference in ventilation and ICU stay between groups. (Table 3)

Discussion

Coronary artery bypass grafting in patients with low EF is challenging. Therefore, we evaluated if preoperative levosimendan could improve the outcomes in those patients. Previous studies showed that levosimendan's benefit was confined to the low EF patients [7, 8]. Starting the treatment with levosimendan before myocardial ischemia will cause a similar effect to ischemic preconditioning [9]. An expert statement recommended the preoperative use of levosimendan one day before surgery in patients with low myocardial function, including right ventricular dysfunction [9]. Preoperative infusion resulted in significant and persistent hemodynamic optimization and increased the tolerance to surgical injury [2,7]. A systematic review revealed that levosimendan's benefits were more pronounced when used preoperative [10].

Table 2: Comparison between the two groups regarding operative data. Data were presented as mean and SD or number (%)

	Group A (n=75)	Group B (n=75)	P-value
Operative time (min)	344±28.7	421.4±34.5	< 0.001
CPB time (min)	97±17.4	127.4±24.5	< 0.001
Cross-clamp time (min)	69.1±13.6	66.4±11.4	0.45
Number of grafts	3± 1	3± 1	>0.99
CPB weaning failure			
First weaning failure	13 (17.3%)	23 (30.7%)	0.06
Second weaning failure	6 (8%)	14 (18.7%)	0.06
Intraoperative IABP	6 (8%)	14 (18.7%)	0.06

CPB: cardiopulmonary bypass; IABP: Intra-aortic balloon pump

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Table 3: Comparison between the two groups regarding postoperative data. Data were presented as mean and SD or number (%)

	Group A (n=75)	Group B (n=75)	P-value
Tachyarrhythmia post-bypass			
Atrial fibrillation	20 (26.7%)	18 (24%)	0.57
Ventricular tachycardia or fibrillation	12 (16%)	15 (20%)	0.4
Hypotension	28 (37.3%)	23 (30.7%)	0.17
Use of inotropes	37 (49.3%)	52 (69.3%)	< 0.001
IABP (postoperative)	5 (6.7%)	8 (10.7%)	0.4
Mechanical ventilation (h)	12±3.3	19.6±4.7	0.04
ICU stay (days)	3.8±1.2	5.3±1.4	< 0.001
Hospital stay (days)	9.4±1.6	10.6±2.7	0.73
Pre-discharge EF (%)	55.4±5.2	53.8±6.5	0.65
Mortality	10 (13.3%)	18 (24%)	0.09

EF: ejection fraction, IABP: intra-aortic balloon pump; ICU: intensive care unit

On the other hand, intraoperative use of levosimendan led to a reduction in the rate for reintubation, ICU and hospital stay time, a lower incidence of sepsis, and a lower mortality rate compared to the postoperative use [1,11].

The recommended dose of levosimendan is 0.1 µg/kg/min infusion for 24 h with a starting bolus dose of 12 µg/kg in 10 min Infusion. Toller and associates advised against the bolus dose when used preoperatively, as there is enough time to get the drug's best plasma level [9]. However, when used intraoperatively, patients who received the bolus dose followed by infusion had a lower mortality rate [10].

In our study, although the recorded hypotension was not significant between both groups, the need for inotropic support was significantly more frequent in the conventional group. This finding was explained by considering that the hypotension was caused by levosimendan's vasodilatation effect and not a form of LCOS. In seven studies, the levosimendan group had significantly less evidence of LCOS than the placebo group [10]. A placebo-controlled study involving 106 patients reported lower inotropic requirements with the levosimendan group [1]. Additionally, these patients experienced significantly fewer LCOS events and needed less inotropic support after a day of infusion [6]. Furthermore, Levin and colleagues found that fewer patients required the addition of inotropic agents and vasopressors in the levosimendan group versus the control group [7].

There was a difference between both groups regarding the rate of intra-aortic balloon use. After the first weaning attempt's failure, epinephrine was added with resuming bypass and revising blood gases, electrolytes, and temperature. After the failure of the second time, the IABP was inserted. However, this rate was not significant in the ICU as we have decided to insert the IAB as early as possible. Others have demonstrated the same finding as reported by Levin and coworkers that (6.3%) patients treated with levosimendan received an IABP compared to (30.4%) in the control group [7]. Moreover, Severi and associates have supported the benefits of levosimendan over the IABP. Many patients with contraindications to the IABP had the best benefit from levosimendan [12].

The ventilation time was significantly prolonged in the conventional group. This finding was expected because of the higher rate of IABP use, the more frequent LCOS, and the more need for inotropes in this group. Similar data were reported in a study involving 106 patients where the levosimendan group showed lower myocardial injury and decreased time on the ventilator [1]. Furthermore, in a meta-analysis, four studies that included 165 patients with low preoperative EF showed a significantly shorter ventilation duration

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in the Levosimendan group than the placebo group [10].

In the present study, the duration of ICU and hospital stay were shorter with levosimendan. This was explained by the early mortality cases, which were eliminated during the calculation of the length of stay. A meta-analysis of eight studies investigated the length of ICU stay, and patients who received levosimendan showed significantly less stay-time in the ICU than placebo cohort. There was no significant difference in both groups in terms of the length of hospital stay [10]. The earlier infusion of levosimendan protects the myocardium and the other body organs and subsequently reduces the rate of complications after cardiac surgery in patients with compromised cardiac function [11]. Furthermore, the perioperative use of levosimendan in high-risk patients was associated with significantly less ICU stay when compared with the IABP [12].

We found a reduction in mortality in the levosimendan group. We have noticed that most mortality cases were those patients who faced the difficulty of weaning from CPB. This finding supports the benefit of early levosimendan utilization. Many authors reported the same results with a significant reduction in mortality in levosimendan versus control groups [7, 8, 10, 13].

Moreover, in studies comparing the intraoperative versus the ICU use of the drug, they found a significant reduction in early mortality [11]. Other authors reported a non-significant reduction in deaths in the levosimendan group [6]. A recent meta-analysis concluded that levosimendan reduced mortality but not to a significant level [14].

Levosimendan side effects:

One of the most frequent adverse effects of levosimendan is a headache. The incidence of headaches in such patients was up to 40% [15]. The presence of headaches was not significant among our patients. When present, it was relieved by simple analgesics.

The incidence of significant hypotension was higher in the levosimendan group (37.3% versus 30.7%). This problem was obvious when using the initial loading dose or after developing low cardiac output. It was associated with increased demands for high doses of vasoconstrictor agents with harmful renal perfusion effects. Eriksson and coworkers reported the same results. They noticed that vasoconstrictors use was significantly higher in the levosimendan group [16].

The evidence regarding levosimendan to cause arrhythmia is conflicting. There was no significant difference between both groups regarding the development of AF, VT, or VF. Many authors observed similar results [6, 13].

The SURVIVE trial compared levosimendan's efficacy and safety versus dobutamine in acute myocardial dysfunction in 1327 patients. In the levosimendan group, patients were more likely to experience atrial fibrillation with a non-significant difference in developing ventricular tachycardia [16]. Furthermore, A higher incidence of ventricular arrhythmias was noticed in the levosimendan group versus placebo in the REVIVE trial [17].

Limitations of the study:

The detailed preoperative data of coronary artery anatomy, previous stenting, and preoperative myocardial infarction events were not analyzed. The type of cardioplegia was not uniform as in many cases we used HTK solution. The sharp definition of LCOP and the decision of IABP placement or adding additional inotropes were not standardized.

Conclusion

The preoperative use of levosimendan could improve the outcomes in patients undergoing coronary artery bypass surgery with low ejection fraction. Levosimendan complication profile was comparable to the conventional approach.

Conflict of interest: Authors declare no conflict of interest.

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