



The Role of Perioperative Levosimendan in Patients with Reduced Ejection Fraction undergoing Cardiac surgery in Reducing Post-operative Hemodynamic Support

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Abstract

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BACKGROUND: Acute perioperative left ventricular dysfunction is a major complication affecting patients subjected to cardiac surgery and is associated with increased mortality. Levosimendan as a “calcium sensitizers” with inodilator effect improves myocardial contractility by sensitizing troponin C to calcium without increasing myocardial oxygen consumption and without impairing relaxation and diastolic function.

AIM: The aim of this study was to evaluate the effect of perioperative levosimendan compared to the conventional management used in the patient with poor left ventricular function undergoing cardiac surgery to reduce the need of post-operative pharmacological and mechanical circulatory support.

METHODS: It is prospective observational studies were patients undergoing cardiac surgery divided into two groups of 25 patients each. The first group received conventional management while the other group received levosimendan additionally duration and type of post-operative pharmacological support, duration of mechanical ventilation, durations of ICU and hospital stays, and major outcomes, and data about the need of mechanical support were collected.

RESULTS: In the levosimendan, fewer patients required vasoactive agents post-surgery (Noradrenaline) compared to the conventional group, yet the use of inotropic support (adrenaline) in the 2nd day and the need of mechanical circulatory support was equal in both groups. The mortality was equal in both groups.

CONCLUSION: Perioperative levosimendan may reduce the need of vasoactive agents postoperatively, but it does not reduce the need of inotropic nor mechanical support.

Introduction

Acute perioperative left ventricular dysfunction is a major complication affecting from 15 to 20% of patients subjected to cardiac surgery [1], [2], [3], [4], [5] and is usually associated with higher mortality rates, this is mainly due to post-operative global myocardial ischemia with consequences of reperfusion which may result in a state of transient left ventricular dysfunction (myocardial stunning) in the immediate and early post-operative period [3], [6].

Post-operative hemodynamic support either pharmacological management, including vasodilator agents, inotropic and vasoactive therapy, as well as mechanical support, including intra-aortic balloon counter pulsation (IABP), Venous Arterial ECMO, and Ventricular Assist Devices, are sometimes used to restore adequate tissue perfusion in the early post-operative period.⁽²⁾ Postoperatively, the most commonly used inotropes are phosphodiesterase III inhibitors and beta-adrenergic agonists, that is, Adrenaline [7], [8], [9]. However, only limited randomized and controlled trials have shown the superiority of any inotropic agent in

terms of major clinical outcomes. Furthermore, meta-analyses and observational studies suggest that catecholamines and PDE-3 inhibitors may increase mortality [3], [9], [10].

Levosimendan is an inodilator agent and calcium sensitizer, which increases the sensitivity of contractile proteins to calcium. The use of levosimendan in the treatment of decompensated heart failure is based on its positive inotropic action performed by sensitizing troponin C to calcium with no significant increase in the myocardial oxygen consumption [11] and without impairing the diastolic function and relaxation [12]. It is also an ATP-dependent potassium channels opener that works on smooth muscle fibers, which results in a systemic, pulmonary, and coronary vasodilatation and can offer a cardioprotective effects during myocardial ischemia [13], [14], [15].

Many trials and a network meta-analysis suggested levosimendan as an inotrope that can reduce mortality among patients undergoing cardiac surgery [16]. Treatment with levosimendan results in greater cardiac output than using treatment with catecholamines or PDE-3 inhibitors, it also has a beneficial effect on

myocardial oxygen consumption [3], [17]. Moreover, it has antioxidant and anti-inflammatory [17]. Accordingly, it is widely used in several countries and cardiac surgery centers.

Our aim was to evaluate the effect of levosimendan compared to conventional pharmacological management in reducing the need of post-operative pharmacological and mechanical circulatory support and the length of ICU stay in patients undergoing cardiac surgery with reduced ejection fraction.

Patients and Methods

We conducted a prospective observational cohort study, from the period of March 2017 to January 2019 in three cardiac surgery centers, in which patients admitted to the intensive care unit following cardiac surgery with reduced pre-operative ejection fraction. The trial protocol for data collection was approved by the ethics committee of critical care department, Cairo University.

Seventy patients were evaluated to be enrolled in the study, 20 of them were excluded as did not meet the inclusion criteria. A total of 50 patients were enrolled in our study, 25 of them received levosimendan as an inotrope and the other 25 patients received conventional pharmacological management including inotropic support (Adrenaline and noradrenaline) and mechanical circulatory support according to the medical need of the patients and local hospital protocol.

We collected pre-operative data on baseline characteristics and coexisting conditions, intraoperative and post-operative treatment data, post-operative immediate and follow-up hemodynamics monitoring data and laboratory values, duration and type of post-operative pharmacological support, duration of mechanical ventilation, durations of ICU and hospital stays, and major outcomes; we also collected data about the need of mechanical support.

Outcome measures

Our primary outcomes were as follows:

1. The need for post-operative inotropic agents (adrenaline) beyond 48 h after the initiation of the study treatment.
2. The need of vasoactive agents (noradrenaline) in the early post-operative phase.
3. The need for post-operative mechanical circulatory support (intra-aortic balloon pump) or failure to wean from this technique (at 96 h following initiation of the study treatment) if they were inserted preoperatively.

Secondary outcome measures

The secondary outcomes are follows:

1. Compare mortality among both groups of patients.
2. Evaluate the effects of levosimendan treatment on ICU length of stay, the duration of mechanical ventilation and the need of renal replacement therapy.
3. The immediate effect on laboratory post-operative markers of perfusion (base deficit and mixed central venous saturation).

Statistics methods

Data were collected, revised, coded, and entered to the Statistical Package for the Social Science (IBM SPSS) version 20 and the following were done:

Qualitative data were presented as number and percentages, while quantitative data were presented as mean, standard deviations, and ranges. The comparison between two groups with qualitative data were done using Chi-square test. The comparison between two independent groups with quantitative data and parametric distribution was done using independent t-test, while the Mann–Whitney U-test done for two independent samples with non-parametric distribution and the comparison between more than two groups with quantitative data and parametric distribution was done using one-way ANOVA test, while the Kruskal Wallis test done for more than two groups with quantitative data with non-parametric distribution.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. Hence, p-value was considered significant as the following:

- $p > 0.05$: Non-significant
- $p < 0.05$: Significant.

Results

Trial population and baseline characteristics and operative data

Seventy patients who were admitted to the Critical Care Department after for cardiac surgery with reduced ejection fraction and started inotropic agents for hemodynamic support were evaluated to be enrolled in the study, 20 of them were excluded as they met the exclusion criteria or did not meet the inclusion criteria 25 patients received levosimendan and 25 patients received conventional management (Figure 1).

The mean age of our study population was 60 ± 9.39 years with range of 33–76 years as presented. We did not find any statistical significant difference between both study groups regarding the mean age

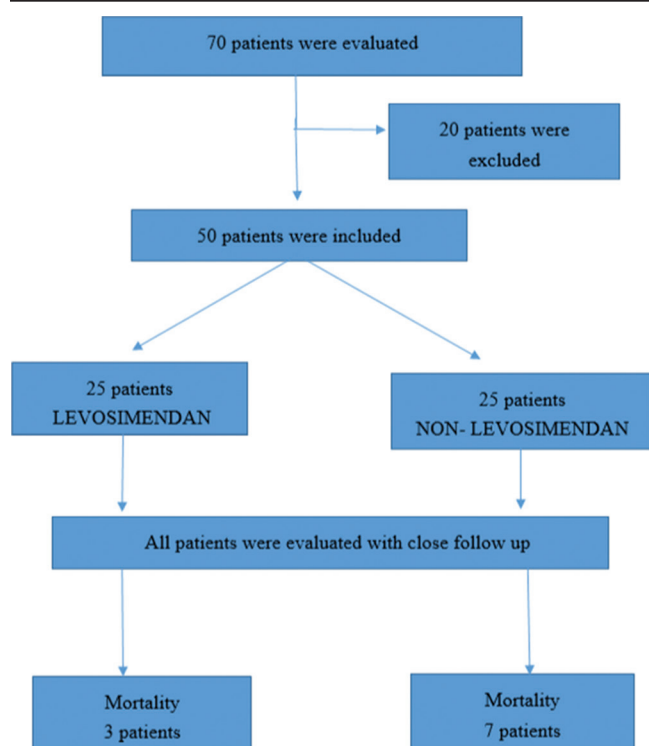


Figure 1: Flow chart of the study

(61 ± 9.9 years versus of 59 ± 9 years, respectively) with p -value = 0.457 as presented in Table 1. We did not find any statistical difference in the base line characteristics between both groups except for the higher prevalence of diabetes in the levosimendan group (Table 1).

Table 1: Characteristics of patients and operation

Characteristic	Levosimendan N = 25	Conventional N = 25	p value
Age (years)	59 ± 9	61 ± 9.9	0.45
Male gender	18 (72%)	21 (84%)	0.248
BMI	32.1 ± 4.3	32.3 ± 7	0.89
DM	22 (88%)	16 (64%)	0.045
Hypertension	19 (74%)	13 (52%)	0.07
Chronic kidney disorder	7 (28%)	6 (24%)	0.5
Pre-operative EF (%)	$32. \pm 4.3$	31.1 ± 3.5	0.48
On pump surgery	9 (36%)	19 (76 ± %)	0.005

There was a statistically significant difference regarding the use of bypass machine between the two groups, as the conventional group had 19 patients (76%) required bypass machine (on pump) and six patients (24%) were off bypass machine (off pump), while the levosimendan group had nine patients (36%) required bypass machine (on pump), and 16 patients (64%) were off bypass machine (off pump) ($p = 0.005$), as shown in Table 1.

Post-operative ejection fraction (EF%)

There was no statistically significant difference regarding the post-operative mean ejection fraction between the two groups, in the conventional group, mean post-operative EF% was $36.3 \pm 4.5\%$ versus $38.2 \pm 4.2\%$ in the levosimendan group ($p = 0.133$), as shown in Table 2.

Table 2: Outcomes of the study

Outcome	Levosimendan N = 25	Conventional N = 25	p value
Markers of perfusion			
Post-operative base excess/deficit (mmol/L)	$+0.9 \pm 2.5$	-1.6 ± 4.1	0.012
Mixed oxygen venous saturation (%)	69.8 ± 7.3	64.7 ± 8.8	0.029
Post-operative pharmacological support			
Adrenaline (on day 2)	4 (16%)	9 (36%)	0.098
Noradrenaline	3 (12%)	9 (36%)	0.04
Mechanical circulatory support			
IABC	2 (8%)	4 (16%)	0.334
Post-operative EF (%)	38.2 ± 4.2	36.3 ± 4.5	0.133
Length of mechanical ventilation (hours)	72 ± 43.2	100 ± 79.2	0.12
Length of ICU stay (days)	2.5 ± 6.2	8.1 ± 2.8	0.012
In-hospital mortality	3 (12%)	7 (28%)	0.145
Need of RRT	4 (16%)	2 (8%)	0.33

Markers of tissue perfusion

There was a statistically significant higher post-operative base deficit in the conventional group with a mean of -1.6 ± 4.1 (mmol/L) compared to $+0.9 \pm 2.5$ (mmol/L) in the levosimendan group ($p = 0.012$), as shown in Table 2.

There was a statistically significant higher post-operative mixed venous central oxygen saturation in the levosimendan group compared to the conventional group with $p = 0.029$.

Post-operative need for pharmacological hemodynamic support

Regarding the need adrenaline infusion in the 2nd day: In the conventional group, there were nine patients (36%) who were still using adrenaline infusion, while in levosimendan group, only 4 patient (16%) used adrenaline infusion as shown yet this difference was not statistically significant ($p = 0.098$) in Table 2.

Regarding the need of adding another vasoactive agent (Noradrenaline) infusion: In the conventional group, there were nine patients (36%) through which noradrenaline was used to achieve target mean arterial pressure, yet in the levosimendan group, only three patients (12%) used noradrenaline, as shown in Table 2 ($p = 0.04$).

Post-operative mechanical circulatory support

In the present study, a total of six patients (12%) required the use of intra-aortic balloon counter pulsation postoperatively, as shown in Table 1. Four of them were in the conventional group (16%) versus two patients (8%) in the levosimendan group ($p = 0.334$) Table 1.

Duration of mechanical ventilation

There was no statistically significant difference regarding the mean duration of mechanical ventilation between the two groups (p value = 0.120), as shown in Table 2.

Evaluation of length of ICU stay in both groups

The mean length of ICU stay in the conventional group was 8.1 ± 2.8 days, while the Levosimendan group was 6.2 ± 2.5 days ($p = 0.012$), as shown in Table 2.

Evaluation of in-hospital mortality

Our results showed no significant difference in mortality between groups. Seven patients were considered as in hospital mortality in the conventional group versus 3 in the levosimendan group ($p = 0.145$), as presented in Table 2.

Discussion

Patients post-cardiac surgery were always considered to be a subject for observing the beneficial effect of levosimendan, this is due to the transient nature of post-operative myocardial dysfunction [13], [14], [15] and stunning that represents the majority of cases of perioperative heart failure [4], [5]. This phenomenon is usually reversible within 48 h. Due to its pharmacodynamics (increase in cardiac output with modest increase in myocardial oxygen consumption as well as its lusitropic action), levosimendan appeared to be an ideal inotropic agent to support heart function in such patients [13].

In our study, the use of levosimendan compared to conventional management had no significant impact on LV function postoperatively, this was determined by echocardiography measurements of ejection fraction performed in the early post-operative phase. On the other hand, many studies showed an immediate and early improvement of post-operative LV cardiac functions in the group using levosimendan. One of them M khaled *et al.* [18] who conducted an observational study on 60 patients divided into two groups and showed a higher post-operative ejection fraction in the levosimendan group compared to conventional group, also Husedzinovic *et al.*, in a double-blind randomized trial evaluated the effect of levosimendan during off pump coronary artery bypass grafting and enrolled 24 patients receiving either placebo or levosimendan, his results showed that, the cardiac index and the LVEF were significantly higher with levosimendan group compared with placebo [19]. Similarly Leppikangas *et al.* who conducted a randomized VS placebo study on 24 patients evaluating the effect of pre-operative levosimendan infusion in combined aortic valve and coronary bypass surgery, his results did not match with our results and showed higher cardiac index and stroke volume index with levosimendan for the 1st day in post-operative period [20].

Our study used base deficit and mixed central venous saturation as markers for adequate cardiac output and tissue perfusion. There was a statistical significant higher mixed venous saturation and lower base deficit in the early post-operative phase in the group using levosimendan compared to the conventional management group. Similar to our study, Khaled *et al.* [18] who showed higher perfusion markers (base deficit and Svco2) in the levosimendan group compared to the conventional inotropic group and Julian Alvarez *et al.* results also showed a significant difference in mixed venous oxygen saturation at the early post-operative phase between both groups [21]. On the same hand, Malliotakis *et al.* determined that there was significant difference in mixed venous oxygen saturation in the levosimendan infusion group [22]. Furthermore, Shawaf *et al.* who conducted a study enrolling 30 cardiac surgery patients comparing levosimendan VS milrinone in the type2 diabetic patient with low LVEF undergoing elective coronary artery surgery found that there was significantly higher mixed venous oxygen saturation with levosimendan [10].

In our study, the need for post-operative vasoactive support (Noradrenaline) was less in the levosimendan group, yet the need of prolonged inotropic support was equal in both groups Regarding use of adrenaline infusion in the 2nd day, it was also noticed that there was no difference between both groups. Our results go hand by hand with De Hert *et al.* stating that need of noradrenaline was higher in the levosimendan group [23]. Furthermore, Levin *et al.* showed that the levosimendan treated group showed lower requirement for vasopressors [24]. In addition, Tritapepe *et al.* showed that levosimendan infusion for 10 min before initiation of coronary artery bypass grafting (CABG) followed by a post-operative infusion reduced the proportion of patients requiring inotropic support for 12 h [25]. In contrast to our results, Ravikumar Gandham *et al.* showed that there was a significant difference between both groups levosimendan and conventional with 14 patient required norepinephrine and seven patients required adrenaline within the levosimendan group, while two patients required adrenaline, two patients required norepinephrine in the conventional (dobutamine) group [26].

In our study, there was no statistically significant difference between the two groups regarding the need for intra-aortic balloon. This goes in hand with Mehta *et al.* who showed no difference in the need of mechanical circulatory support in both groups [2].

In our study, there was no difference in the length of mechanical ventilation in both groups.

Similar to our results, Khaled *et al.* [18] and Mehta *et al.* [2] who found no difference in the length of mechanical ventilation between both groups. In contrast to our results, Ravikumar Gandham *et al.* who stated a significant difference in mechanical ventilation duration between the two groups [26].

Our study showed a significant difference between both groups regarding length of ICU stay. Supporting our results, Tritapepe *et al.* [25], concluded that, short pre-treatment with levosimendan in patients undergoing myocardial revascularization resulted in a reduction of tracheal intubation time, decreased requirement for inotropic support and thus a shorter duration of ICU stay. On the same way, Tasouli *et al.* [27] compared 45 patients with LCOS treated with levosimendan at two different time points in another randomized study. The patients were treated with inotropes and/or balloon counter pulsation (IABP). The study showed better results in those who were treated earlier with levosimendan, having a shorter time on inotropic support, a lower incidence of sepsis, and a shorter ICU stay and hospital stay. Contrary to our results, Stefan G.De Hert *et al.* stated no difference in ICU stay [24]. Furthermore, Ravikumar Gandham *et al.* had found no difference in ICU stay [26].

Regarding mortality, our results showed no significant difference regarding in hospital mortality between the two study groups. Similar to our results, the meta-analysis Chen *et al.* [28] performed on a total of 25 RCTs enrolling 2,960 his pooled analysis showed that the all-cause mortality rate was 6.4% (71 of 1106) in the levosimendan group and 8.4% (93 of 1,108) in the placebo group [28], also Khaled *et al.* results did not show any mortality differences between both groups [18]. On the other hand, Giovanni Landoni *et al.* [3], [6], a meta-analysis was conducted to determine the impact of levosimendan on mortality. Data from 5,480 patients in 45 randomized clinical trials were analyzed and suggested a lower mortality rate in the levosimendan group.

Limitations

Our study has some limitations. First, being a non-randomized observational study. Second, we investigated a mixed population of patients who were under-going different modalities of cardiac surgeries (the distribution on pump and off pump technique was not equal in both groups). Third, we did not evaluate the post-operative cardiac-output and stroke volume, which could have helped us understand and interpret the effect of drug on hemodynamics and so the results of the trial even better than monitoring the ejection fraction.

Conclusion

The use of perioperative levosimendan reduced the need of post-operative vasoactive agents

(Noradrenaline) and the length of ICU stay, yet it did not decline the need of post-operative inotropic agents (Adrenaline) nor the mechanical circulatory support and it did not show any beneficial effect on mortality.

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