Comparison of prophylactic levosimendan versus intra-aortic balloon pump for off-pump coronary artery bypass grafting in patients with low ejection fraction: A randomized-controlled trial

Ritesh Mate, Noaman Shaikh, Chaitanya Raut, Arnab De, Prashant Mishra

Department of Cardiovascular and Thoracic Surgery, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India

Received: May 26, 2020 Accepted: September 29, 2020 Published online: November 06, 2020

ABSTRACT

Objectives: This study aims to compare the efficacy and short-term clinical outcomes of levosimendan versus intra-aortic balloon pump (IABP) in patients undergoing off-pump coronary artery bypass grafting (OPCABG).

Patients and methods: This prospective, randomized-controlled study included a total of 60 patients (44 males, 16 females; mean age 60.58±5.23 years; range, 42 to 70 years) with low left ventricular ejection fraction (<25%) undergoing OPCABG between January 2019 and September 2019. The patients were divided into two groups as levosimendan (Group L) and IABP (Group B). Hemodynamic parameters were measured at prespecified time points.

Results: Hemodynamic data recorded at baseline were comparable in both groups, while cardiac index progressively increased in both groups. Although, the increase was statistically significant on multiple measures analysis of variance in both groups, no significant difference was observed at different time points. Pulmonary capillary wedge pressure decreased in both groups; however, the decline was not statistically significant. Serum lactate concentration was consistently lower in Group B compared to Group L at all time points. The heart rate, mean arterial pressure, and Vasoactive Inotropic Score (VIS) were comparable in both groups at all time points. The mean length of intensive care unit (ICU) stay was statistically significant in Group B compared to Group L.

Conclusion: The use of prophylactic levosimendan is comparable to prophylactic IABP, when hemodynamic parameters are considered. Prophylactic levosimendan is associated with a shorter length of hospital and ICU stay. Prophylactic levosimendan can be considered an alternative to prophylactic IABP in patients with low ejection fraction in whom IABP is contraindicated.

Keywords: Coronary artery bypass grafting, intra-aortic balloon pump, levosimendan, low ejection fraction, off-pump.
the calcium sensitization of the contractile proteins. It has also been suggested that this drug protects the ischemic myocardium and that it decreases the infarct size in coronary-ligated animals.

In the present study, we aimed to compare the efficacy and short-term clinical outcomes of levosimendan versus IABP in patients with low LVEF undergoing OPCABG.

**PATIENTS AND METHODS**

This prospective, randomized-controlled study was conducted at Lokmanya Tilak Municipal General Hospital and Medical College, Sion, Mumbai between January 2019 and September 2019. The patients who underwent OPCABG with a low LVEF (<25%) were included. Patients undergoing emergency OPCABG or concurrent procedures in addition to OPCABG such as congenital, valve, or aortic surgery, those treated with levosimendan within the past three months or with other inotropes within the previous week were excluded from the study. Patients with significant pulmonary disease, renal dysfunction, liver dysfunction, redo-OPCABG, or arrhythmias with bundle branch block and those who did not survive for 48 h after surgery due to surgery-related causes were also excluded. A written informed consent was obtained from each patient. The study protocol was approved by the Lokmanya Tilak Municipal General Hospital and Medical College Ethics Committee and Institutional Review Board (IEC/38/18). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The LVEF was measured using transthoracic echocardiography (TTE) both preoperatively and postoperatively.

In the given period, we operated 82 patients with low LVEF (<25%), of which 68 patients were eligible for the study, of which only 64 patients consented. Of these, only 60 patients (44 males, 16 females; mean age 60.58±5.23 years; range, 42 to 70 years) survived for 48 h and were included in the study. These 60 patients were divided into two equal groups including 30 in each as follows: levosimendan (Group L) and IABP (Group B). The patients were randomly assigned to the respective groups. Randomization was carried out through the random allocation via computer-generated random numbers.

**Management protocol**

All patients were admitted to the cardiac intensive care unit (ICU) 24 h prior to surgery. A Swan-Ganz catheter was inserted for pulmonary artery pressure monitoring and radial arterial cannulation was performed for systemic arterial monitoring. The levosimendan or IABP therapy was started 24 h prior to surgery in the respective groups.

In Group L, patients received a preoperative dose of levosimendan (Inj. Semenda-12.5 mg/mL, Lupin lab.) 200 μg/kg dose dissolved in 50 mL of normal saline (NS) and started at a rate of 2 mL/h for 24 h.

In Group B, the IABP was inserted through the femoral artery by the percutaneous technique using an 8F IABP catheter (Arrow International, Reading, PA, USA) connected to the Arrow® pump. The position of the balloon was confirmed by radiography. Heparin infusion was started at a rate of 5 to 10 U/kg/h to maintain the activated coagulation time within 140 to 160 sec.

All patients underwent continuous monitoring of heart rate (HR), ambulatory blood pressure (ABP), cardiac index (CI), mean arterial pressure (MAP), and pulmonary capillary wedge pressure (PCWP). Central venous pressure (CVP), urine output, Vasoactive Inotropic Score (VIS), and lactate levels were also monitored. Hemodynamic parameters recorded at various time points before or after the drug were administered or IABP was inserted. All the parameters were measured at regular time points, i.e., at baseline (T0), 30 min (T1) after beginning levosimendan or IABP, 6 h (T2), 12 h (T3) after starting levosimendan or IABP respectively, prior to induction (T4), 15 min after induction (T5), immediately after completion of revascularization (T6), 6 h after surgery (T7), 12 h after completion of surgery (T8), 24 h after surgery (T9), and 48 h after surgery (T10).

Anesthetic management and surgical procedures were the same in both groups. Induction and maintenance of general anesthesia with endotracheal intubation was standardized in both groups. All procedures were performed using the off-pump technique. The OPCABG was performed using the left internal mammary artery (LIMA) and reversed saphenous vein grafts (rSVGs) as conduits. Left anterior descending (LAD) artery was revascularized by LIMA, while other coronary arterial targets were revascularized by rSVGs via an aortocoronary anastomosis.
Definitions

High inotropic support was defined as the requirement of dobutamine >5 μg/kg/min and/or adrenaline >0.1 μg/kg/min and/or noradrenaline >0.1 μg/kg/min. The VIS was calculated as a weighted sum of all administered inotropes and vasoconstrictors, reflecting pharmacological support of the cardiovascular system.\cite{8} It was calculated using the formula described by Koponen et al.,\cite{9} during the first 48 h after postoperative ICU admission, which were retrieved from the ICU critical care information system.

Low cardiac output syndrome (LCOS) was defined as the presence of low CI (<2.2 L/min/m²) with elevated PCWP (>16 mmHg) and a partial pressure of arterial oxygen (PaO₂) of <60 mmHg. Acute renal failure was defined when serum (S) creatinine increases by >50% from baseline with or without oliguria (urine output <0.5 mL/kg/h) or requiring dialysis.\cite{8}

Cerebrovascular accidents were defined, if there was development of a new focal neurological deficit or coma persisting for >48 h, after metabolic causes were ruled out.\cite{3} A neurological alteration persisting <48 h was considered as a transient ischemic attack. Postoperative mortality was defined as death occurring during hospitalization or within 30 days after surgery.

Statistical analysis

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Student’s t-test and analysis of variance (Wilcoxon signed-rank test) were used to determine the differences between the groups. The multiple measures analysis of variance (ANOVA) was used for within the group analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic data, nature of the disease, and surgical characteristics of all patients were comparable in both groups (Table 1). Baseline hemodynamic parameters and serum lactate concentrations were also comparable in both groups. Hemodynamic data were recorded and compared at various time points. Preoperative ICU stay was uneventful in both groups. Seven patients in Group L developed mild hypotension, which resolved with fluid resuscitation. Two patients (n=1 in each group) required vasopressors support and one patient in Group B required removal of IABP due to limb ischemia and re-insertion of IABP in the opposite femoral artery.

| Table 1 | Baseline demographic and clinical characteristics of patients |
|---------|-------------------------------------------------------------|
|         | Levosimendan (Group L) (n=30) | IABP (Group B) (n=30) |
| Variable | n | Mean±SD | n | Mean±SD | p |
| Age (year) | 30 | 60.2±5.7 | 30 | 161.2±8.5 | 0.55 |
| Sex | | |  |  |  |
| Male | 23 |  | 21 | |  |
| Female | 7 |  | 9 | |  |
| Height (m) | | 162.4±7.3 | | | |
| Weight (kg) | | 65.6±6.3 | | 66.6±6.9 | 0.56 |
| Hypertension (%) | 19/30 | 20/30 | 0.78 |
| Diabetes mellitus | 21/30 | 22/30 | 0.77 |
| Left ventricular ejection fraction | 20.5±4.4 | 20.4±4.52 | 0.93 |
| Number of grafts | 2.6±0.8 | 2.5±0.8 | 0.64 |
| Baseline serum creatinine (mg/dL) | 1.1±0.2 | 1.2±0.1 | 0.15 |
| Hemoglobin (%) | 13.5±0.8 | 13.4±0.8 | 0.62 |

IABP: Intra-aortic balloon pump; SD: Standard deviation.
Hemodynamic data recorded at baseline were comparable in both groups (Tables 2, 3). A progressive increase in the CI was observed in both groups. The increase was observed to be statistically significant on within the group in both groups. However, the differences in the CI at different time points between

**Table 2**

| Time   | HR     | MAP     | VIS    |
|--------|--------|---------|--------|
| Time 0 | Group L 70.8±7.1 | 90.2±4.3 | 1.9±0.4 |
| Group B 71.9±8.3 | 88.4±6.6 | 1.7±0.6 |
| P       0.59   | 0.21   | 0.17   |
| Time 1  | Group L 78.2±7.1 | 84.1±6.1 | 1.8±0.5 |
| Group B 77.9±8.3 | 86.1±7.2 | 1.6±0.3 |
| P       0.86   | 0.24   | 0.06   |
| Time 2  | Group L 68.8±5.3 | 86.1±5.3 | 1.6±0.5 |
| Group B 70.7±6.3 | 83.3±6.4 | 1.6±0.9 |
| P       0.22   | 0.15   | 1      |
| Time 3  | Group L 74.8±6.1 | 85.4±6.9 | 1.8±0.8 |
| Group B 74.7±7.3 | 88.5±7.2 | 1.7±0.8 |
| P       0.91   | 0.1    | 0.63   |
| Time 4  | Group L 80.2±4.3 | 88.5±4.1 | 2.1±0.9 |
| Group B 78.9±6.6 | 87.4±6.4 | 2.3±1.1 |
| P       0.32   | 0.43   | 0.44   |
| Time 5  | Group L 88.2±7.1 | 82.2±8.0 | 5.7±2.1 |
| Group B 90.8±4.3 | 80.4±7.2 | 6.4±1.8 |
| P       0.09   | 0.36   | 0.17   |
| Time 6  | Group L 84.2±7.1 | 88.8±5.9 | 6.3±2.3 |
| Group B 83.9±8.4 | 86.6±6.6 | 6.9±2.7 |
| P       0.87   | 0.9    | 0.35   |
| Time 7  | Group L 75.2±9.2 | 88.4±5.9 | 6.4±2.1 |
| Group B 76.9±8.5 | 86.5±6.4 | 7.1±2.6 |
| P       0.46   | 0.21   | 0.25   |
| Time 8  | Group L 76.2±8.1 | 88.4±5.9 | 5.4±1.8 |
| Group B 75.6±8.3 | 86.3±6.4 | 6.1±2.3 |
| P       0.77   | 0.19   | 0.19   |
| Time 9  | Group L 68.8±4.3 | 84.1±6.1 | 3.7±1.3 |
| Group B 69.2±6.2 | 86.1±7.2 | 4.2±1.5 |
| P       0.81   | 0.24   | 0.17   |
| Time 10 | Group L 66.5±5.1 | 88.7±5.9 | 1.9±0.8 |
| Group B 65.5±6.3 | 87.5±6.8 | 1.7±1.1 |
| P       0.5    | 0.47   | 0.42   |

HR: Heart rate; MAP: Mean arterial pressure; VIS: Vasoactive Inotropic Score; SD: Standard deviation.

**Table 3**

| Time   | PCWP     | CI     | Lactates |
|--------|----------|--------|----------|
| Time 0 | Group L 20.5±2.5 | 2.1±0.2 | 1.7±0.4 |
| Group B 19.2±3.0 | 2.1±0.2 | 1.8±0.6 |
| P       0.08   | 0.55   | 0.68   |
| Time 1  | Group L 15.9±2.5 | 2.2±0.2 | 1.7±0.3 |
| Group B 12.7±2.4 | 2.2±0.2 | 1.7±0.4 |
| P       <0.0001* | 0.57   | 0.9    |
| Time 2  | Group L 16.3±3.27 | 2.1±0.3 | 1.6±0.2 |
| Group B 15.6±1.26 | 2.2±0.4 | 1.7±0.6 |
| P       0.27   | 0.38   | 0.72   |
| Time 3  | Group L 15.6±3.7 | 2.3±0.2 | 1.8±0.1 |
| Group B 15.0±2.8 | 2.2±0.3 | 1.6±0.5 |
| P       0.41   | 0.09   | 0.08   |
| Time 4  | Group L 15.2±4.3 | 2.1±0.2 | 2.0±0.2 |
| Group B 16.7±3.9 | 2.1±0.2 | 1.8±0.8 |
| P       0.15   | 0.24   | 0.13   |
| Time 5  | Group L 14.3±3.3 | 2.2±0.2 | 1.8±0.4 |
| Group B 14.7±2.3 | 2.2±0.1 | 1.7±0.5 |
| P       0.67   | 0.48   | 0.27   |
| Time 6  | Group L 15.3±3.3 | 2.2±0.1 | 1.7±0.3 |
| Group B 14.6±2.3 | 2.2±0.3 | 1.6±0.6 |
| P       0.33   | 0.85   | 0.56   |
| Time 7  | Group L 16.3±3.2 | 2.2±0.2 | 1.6±0.3 |
| Group B 15.7±1.6 | 2.2±0.2 | 1.5±0.7 |
| P       0.35   | 0.84   | 0.22   |
| Time 8  | Group L 15.6±3.7 | 2.2±0.1 | 1.7±0.2 |
| Group B 14.2±1.6 | 2.2±0.2 | 1.7±0.5 |
| P       0.18   | 0.09   | 0.54   |
| Time 9  | Group L 16.3±3.3 | 2.2±0.3 | 1.6±0.4 |
| Group B 15.7±1.6 | 2.2±0.2 | 1.5±0.9 |
| P       0.32   | 0.47   | 0.35   |
| Time 10 | Group L 16.3±3.2 | 2.3±0.1 | 1.6±0.3 |
| Group B 15.6±1.3 | 2.2±0.2 | 1.5±0.7 |
| P       0.29   | 0.12   | 0.19   |

PCWP: Pulmonary Capillary Wedge Pressure; CI: Cardiac Index; SD: Standard deviation.
the two groups were not statistically significant. The
PCWP decreased in both groups; however, the decline
was not statistically significant, either. Serum lactate
concentration was consistently lower in Group B
compared to Group L at all time points. However, this
difference was not statistically significant. The HR,
MAP, and VIS were comparable in both groups at all
time points.

The mean ICU stay in Group B was 6.5±0.1 days
compared to Group L (4.4±0.2 days), indicating
a statistically significant difference (p<0.001). The
patients in Group B had delayed hospital discharge at
13.4 days, compared to Group L (10.2 days), indicating
a statistically significant difference (p<0.001).

Two patients in Group B required femoral artery
embolectomy due to development of acute thrombosis.
None of the patients in Group L and Group B developed
acute kidney injury. The incidence of postoperative atrial fibrillation was lower in Group L, compared
to Group B, indicating a statistically significant
difference (p=0.01). Noradrenaline requirement
(%) and incidence of LCOS were similar in both
groups. Totally, two patients (one in each group)
died due to sepsis and multiple organ dysfunction.
The length of ICU and hospital stay were higher
in Group B, compared to Group L, indicating a
statistically significant difference (p=0.001).

**DISCUSSION**

Off-pump coronary artery bypass grafting involves
displacement and manipulation of heart to expose
target coronary arteries, particularly obtuse marginal
and posterior descending coronary arteries. This
manipulation may be accompanied by transient annular
mitral distortion, leading to acute mitral regurgitation,
compression of pulmonary veins and/or the right
ventricle in addition to superimposed impaired cardiac
contractions due to the epicardial stabilizer. This results
in hemodynamic instability in the form of increased
filling pressures, right ventricular end-diastolic
pressure and transient diastolic dysfunction.\(^{[10,11]}\) All
these changes are exaggerated intraoperatively in
patients with LV dysfunction, which is the main risk
factor for intra- and postoperative LCOS.\(^{[12,13]}\)

The main challenge during OPCABG is to
maintain optimum hemodynamics. This can be
achieved by mechanical or pharmacological means.
Use of inotropes constitutes major pharmacological
intervention and its appropriate selection helps in
better clinical outcomes. However, conventional
inotropes such as beta-agonists and phosphodiesterase
inhibitors are associated tachycardia and arrhythmia,
leading to an increased myocardial oxygen demand.\(^{[14]}\)

Levosimendan is a novel inotropic agent. It
also provides beneficial immunomodulatory,
cardioprotective, anti-stunning, anti-ischemic, anti-
inflammatory, and antioxidant effects to improve
cardiac performance in the presence of ischemia.\(^{[15-18]}\)
All these characteristics make it a near-ideal inotrope
in patients with LV dysfunction.

The IABP counter pulsation is currently the
most used mechanical assistance device for patients
with cardiogenic shock due to acute myocardial
infarction. Its beneficial physiological effects have been established. The IABP increases diastolic blood pressure,[19,20] and, thus, it improves diastolic coronary perfusion. Furthermore, it increases cardiac output and stroke volume by reducing afterload. The ability to act on diastolic pressure has a great importance in clinical practice, since the elevated diastolic pressure results in a redistribution of coronary blood flow toward ischemic areas of the myocardium. [21]

A multi-center study showed that prophylactic use of IABP improved outcomes in high-risk cardiac patients.[22] The main disadvantages of IABP, particularly in patients with systemic atherosclerosis, is the development of complications associated with instillation of the balloon including includes limb ischemia, damage to the vessels, and bleeding.[23,24]

This study highlights the favorable hemodynamic profile of levosimendan and IABP in terms of reduced PCWP and improved CI after its administration. We consistently observed higher CI in patients treated with IABP during intra- and postoperative period, compared to levosimendan; however, the increase was not statistically significant. The rise in CI leads to reduced serum lactate concentrations, indicating improved microcirculation at peripheral tissue level. Although data are scarce regarding the use of levosimendan during cardiac surgery in patients with low EF, our results are consistent with the recent studies.[24] In a meta-analysis, Landoni et al.[21] emphasized that the use of levosimendan contributed to a significant reduction of mortality in cardiac patients with favorable outcomes. In the study conducted by Alvarez et al.,[25] they concluded that a loading dose of levosimendan needed to be omitted in decompensated heart failure patients to prevent hypotensive episodes. Hence, we preferred an approach of gradually achieving the therapeutic concentration without causing any hypotensive episodes in our institution.

In the current study, none of the patients developed significant hypotension, any hemodynamic instability, and other side effects such as nausea and headache in the preoperative period and the regime was tolerated well. Immediate postoperative outcomes also improved in the levosimendan group with a notably reduced incidence of postoperative atrial fibrillation which can be attributed to antioxidant and anti inflammatory properties of levosimendan.[21] Although several studies have emphasized the increased incidence of ventricular arrhythmias after administration of levosimendan, we found no similar result in our study.

In their study, Baysal et al.[26] suggested that levosimendan increased renal blood flow by decreasing renal vascular resistance and increasing glomerular filtration rate. In another study using propensity score analysis, Lorusso et al.[27] concluded that patients with IABP support in the preoperative period had a lower risk of acute kidney injury. Our findings are also consistent with the aforementioned studies, as none of our patients developed acute kidney injury requiring dialysis.

Furthermore, we observed a decreased incidence of LCOS in both groups. These findings can be attributed to favorable surgical conditions produced by levosimendan and IABP owing to improved myocardial contractility and reduced pulmonary pressures which make the heart supple and easy to operate upon. In another study, Lomivorotov et al.[28] compared levosimendan and IABP in high-risk cardiac surgery patients and concluded that the infusion of levosimendan after anesthesia induction in cardiac surgical patients contributed to lower cardiac troponin I concentrations and improved hemodynamics compared to preoperative IABP. Similarly, Severi et al.[29] also observed a shorter ICU stay in patients pretreated with levosimendan compared to patients receiving prophylactic IABP. In our study, we found a significant difference in the length of ICU and hospital stay between the two groups. The patients in Group B stayed in the ICU for a longer duration (mean 6.5±0.1 days) compared to the patients in Group L (mean 4.6±0.2 days) group. Although two patients in Group B needed an additional procedure in the form of an embolectomy, it did not influence the total ICU stay in the study population.

The single-center design is the main limitation of the present study. In addition, we were unable to consider serum-specific cardiac markers (troponin levels) which would in detail highlight the cardiac status of the patients in both groups. Also, the immediate postoperative mortalities (within 48 h) were unable to be analyzed.

In conclusion, the use of prophylactic levosimendan is comparable to prophylactic IABP, when hemodynamic parameters are taken into consideration. Prophylactic levosimendan is associated with lower hospital and ICU stay. Prophylactic levosimendan can be considered as an alternative to prophylactic IABP in patients with low ejection fraction in whom IABP is contraindicated.
Declarations of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Caparrelli DJ, Ghazoul M, Dietrich EB. Indications for coronary artery bypass grafting in 2009: what is left to surgery. J Cardiovasc Surg (Torino) 2009;50:19-28.

2. Chernov SA. Early postoperative complications and prevention of them in ischemic heart disease patients after direct myocardial revascularization. Ter Arkh 2002;74:45-9.

3. Eriksson O, Pollesello P, Haikal A. Effect of levosimendan on balance between ATP production and consumption in isolated perfused guinea-pig heart before ischemia or after reperfusion. J Cardiovasc Pharmacol 2004;44:316-21.

4. Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. Clin Pharmacokinet 2007;46:535-52.

5. Dernellis J, Panaretou M. Effects of levosimendan on restrictive left ventricular filling in severe heart failure: a combined hemodynamic and Doppler echocardiographic study. Chest 2005;128:2633-9.

6. Tritapepe L, De Santis V, Vitale D, Santulli M, Morelli A, Nofroni I, et al. Preconditioning effects of levosimendan in coronary artery bypass grafting--a pilot study. Br J Anaesth 2006;96:694-700.

7. Grossini E, Molinari C, Caimmi PP, Uberti F, Vacc G. Levosimendan induces NO production through p38 MAPK, ERK and Akt in porcine coronary endothelial cells: role for mitochondrial K(ATP) channel. Br J Pharmacol 2009;156:250-61.

8. Desai PM, Sarkar MS, Umbarkar SR. Prophylactic preoperative levosimendan for off-pump coronary artery bypass grafting in patients with left ventricular dysfunction: Single-centered randomized prospective study. Ann Card Anaesth 2018;21:123-8.

9. Koponen T, Karttunen J, Musialowicz T, Pietiläinen L, Uusaro A, Lahtinen P. Vasoactive-inotropic score and the prediction of morbidity and mortality after cardiac surgery. Br J Anaesth 2019;122:428-36.

10. Mathison M, Edgerton JR, Horswell JL, Akin JJ, Mack MJ. Analysis of hemodynamic changes during beating heart surgical procedures. Ann Thorac Surg 2000;70:1355-60.

11. Mishra M, Malhotra R, Mishra A, Meharwal ZS, Trehan N. Hemodynamic changes during displacement of the beating heart using epicardial stabilization for off-pump coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2002;16:685-90.

12. Rao V, Ivanov J, Weisel RD, Ikonomidis JS, Christakis GT, David TE. Predictors of low cardiac output syndrome after coronary artery bypass. J Thorac Cardiovasc Surg 1996;112:38-51.

13. Açıl T, Türköz R, Açıl M, Sezgin AT, Baltali M, Gülcan O, et al. Value of prolonged QRS duration as a predictor of low cardiac output syndrome in patients with impaired left ventricular systolic function who undergo isolated coronary artery bypass grafting. Am J Cardiol 2006;98:1357-62.

14. Packer M. The search for the ideal positive inotropic agent. N Engl J Med 1993;329:201-2.

15. du Toit EF, Genis A, Opie LH, Pollesello P, Lochner A. A role for the RISK pathway and K(ATP) channels in pre- and post-conditioning induced by levosimendan in the isolated guinea pig heart. Br J Pharmacol 2008;154:41-50.

16. Jamali IN, Kersten JR, Pagel PS, Hettrick DA, Wartliet DC. Intracoronary levosimendan enhances contractile function of stunned myocardium. Anesth Analg 1997;85:23-9.

17. Levijoki J, Pollesello P, Kaheinen P, Haikala H. Improved survival with simendan after experimental myocardial infarction in rats. Eur J Pharmacol 2001;419:243-8.

18. Liu T, Li G, Xu G. Levosimendan may prevent postoperative atrial fibrillation through anti-inflammatory and antioxidative modulation. J Cardiothorac Vasc Anesth 2009;23:757-8.

19. Landoni G, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, et al. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med 2012;40:634-46.

20. Shah B, Sharma P, Brahmbhatt A, Shah R, Rathod B, Shastri N, et al. Study of levosimendan during off-pump coronary artery bypass grafting in patients with LV dysfunction: a double-blind randomized study. Indian J Pharmacol 2014;46:29-34.

21. Landoni G, Lomivorotov VV, Alvaro G, Lobreglio R, Pisano A, Guarracino F, et al. Levosimendan for hemodynamic support after cardiac surgery. N Engl J Med 2017;376:2021-31.

22. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002;360:196-202.

23. Moiseyev VS, Pöder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J 2002;23:1422-32.

24. Abacilar AF, Dogan OF. Levosimendan use decreases atrial fibrillation in patients after coronary artery bypass grafting: a pilot study. Heart Surg Forum 2013;16:E287-94.

25. Alvarez J, Bouzada M, Fernández AL, Caruezo V, Taboada M, Rodriguez J, et al. Hemodynamic effects of levosimendan compared with dobutamine in patients with low cardiac output after cardiac surgery. Rev Esp Cardiol 2006;59:338-45.

26. Baysal A, Yanartas M, Dogukan M, Gundogus N, Kocak T, Koksal C. Levosimendan improves renal outcome in cardiac surgery: a randomized trial. J Cardiothorac Vasc Anesth 2014;28:586-94.
27. Lorusso R, Gelsomino S, Carella R, Livi U, Mariscalco G, Onorati F, et al. Impact of prophylactic intra-aortic balloon counter-pulsation on postoperative outcome in high-risk cardiac surgery patients: a multicentre, propensity-score analysis. Eur J Cardiothorac Surg 2010;38:585-91.

28. Lomivorotov VV, Boboshko VA, Efremov SM, Kornilov IA, Chernyavskiy AM, Lomivorotov VN, et al. Levosimendan versus an intra-aortic balloon pump in high-risk cardiac patients. J Cardiothorac Vasc Anesth 2012;26:596-603.

29. Severi L, Lappa A, Landoni G, Di Pirro L, Luzzi SJ, Caravetta P, et al. Levosimendan versus intra-aortic balloon pump in high-risk cardiac surgery patients. J Cardiothorac Vasc Anesth 2011;25:632-6.