Aims and Objectives: University teaching hospital, randomized control to compare the hemodynamic effects and immediate postoperative outcomes with levosimendan and dobutamine in patients with moderate to severe LV dysfunction undergoing off-pump coronary artery bypass grafting (OPCAB). Settings and Design: University teaching hospital, randomized control study. Materials and Methods: Eighty patients were randomly divided into two groups of 40 each. Group I received levosimendan at 0.1 µg/kg/min and Group II received dobutamine at 5 µg/kg/min. Hemodynamic data were noted at 30 min, during obtuse marginal grafting, 1, 6, 12, and 24 h after surgery. Heart rate (HR), mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI), left ventricular stroke work index (LVSWI) and right ventricular stroke work index (RVSWI), mixed venous oximetry (SvO₂), and lactate were measured. Statistical Analysis Used: Chi-square and Student’s t-test. Results: The HR, MAP, PCWP, SVRI, and PVRI were lower in Group I when compared to Group II. Group I patients showed a statistically significant increase in LVSWI, RVSWI, CI, and PCWP levels when compared to Group II. Comparatively, Group I patients maintained higher SvO₂ and lower lactate levels. Duration of ventilation, Intensive Care Unit (ICU), and hospital stay were lower in Group I. Conclusions: Levosimendan was associated with statistically significant increase in indices of contractility (CI, LVSWI, and RVSWI) and decrease in PCWP during and after OPCAB. Levosimendan group had lower incidence of atrial fibrillation, shorter length of ICU, and hospital stay.

Keywords: Cardiac index, dobutamine, Intensive Care Unit stay, levosimendan, mixed venous oximetry, stroke work index

Introduction

Chronic heart failure (CHF), a clinical syndrome in which abnormalities of ventricular function and neurohormonal regulation lead to pulmonary venous congestion, exercise intolerance, and decreased life expectancy, remains the one major cardiovascular disorder that has increased both in incidence and prevalence in recent years.[1] Severe left ventricular (LV) dysfunction has been reported as an independent predictor of operative mortality in patients undergoing coronary artery bypass grafting (CABG). Off-pump coronary artery bypass grafting (OPCAB) has theoretical and practical advantages over conventional CABG in this subset of high-risk patients.[2] Anesthetic and hemodynamic management of patients undergoing OPCAB with poor LV function remains a challenge. Given the rapid evolution of standard therapy and the frequency with which CHF patients present to the operating rooms and Intensive Care Units (ICUs), anesthesiologists are obliged to know contemporary “best practices” to make appropriate diagnostic and treatment choices.

Dobutamine, a traditional beta-receptor agonist, is the most commonly used agent to increase myocardial contractility. However, distinct clinical disadvantages exist when using this class of drugs (tachycardia, arrhythmias, increased myocardial oxygen demand).

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While phosphodiesterase inhibitors (PDEi) such as milrinone increase myocardial contractility, this class of drugs is also associated with distinct clinical disadvantages (arrhythmias, sometimes excessive systemic vasodilation). Levosimendan, a member of a new class of drugs – calcium sensitizers – may offer substantial clinical advantages over traditional beta-receptor agonists and PDEi by increasing myocardial contractility without initiating tachycardia or arrhythmias, nor increasing myocardial oxygen demand. In addition to being effective in postoperative rescue therapy for patients with difficulty in weaning from cardiopulmonary bypass (CPB), initiation of levosimendan in patients with compromised LV function appears to reduce catecholamine requirements, need for mechanical circulatory support, and duration of critical care.[3]

The aim of the present study was to compare levosimendan versus dobutamine in patients with moderate to severe LV dysfunction undergoing OPCAB. We also compared the outcomes in terms of incidence of postoperative atrial fibrillation (AF), duration of ventilation, ICU, and hospital stay.

Materials and Methods

The study was approved by the hospital ethics committee. Eighty patients were randomly divided into two groups of 40 each. All patients between 30 and 65 years, with moderate to severe LV dysfunction scheduled for OPCAB, were included in the study. Patients with moderate to severe mitral regurgitation, redo or emergency CABG, patients receiving preoperative pharmacological or mechanical support were excluded from the study. Written informed consent was obtained from all the patients. Randomization was done by computerized allocation of patients to both groups. Group I received levosimendan at 0.1 µg/kg/min and Group II received dobutamine at 5 µg/kg/min after anesthetic induction.

The anesthetic technique was standardized for all patients. All the patients received oral diazepam 0.15 mg/kg and pantoprazole 40 mg previous night and on the morning of surgery. Anesthesia was induced by fentanyl 5 µg/kg, etomidate 0.2 mg/kg, sevoflurane 1.4 minimum alveolar concentration, midazolam 50 µg/kg, and maintained by air/oxygen and sevoflurane. Neuromuscular blockade was achieved with vecuronium bromide in a dose of 100 µg/kg for intubation and 20 µg/kg at regular intervals.

As per our institutional protocol, radial and femoral arterial cannulation was performed, along with Swan Ganz thermomix catheterization for pulmonary artery pressure and cardiac output monitoring [Philips Intellivue MP40] in all the cases. OPCAB was performed using Octopus 3 or 4 or Evolution (Medtronic Inc.) stabilizing devices to achieve target coronary artery stabilization by the same surgeon. Posterior and lateral target coronary arteries were accessed after deep pericardial traction sutures. A mean arterial pressure (MAP) was maintained more than 60 mm of Hg throughout the procedure. The coronary artery grafting strategies were to graft left internal thoracic artery to LAD artery first, followed by either obtuse marginal (OM) arteries or right coronary artery whichever was critically stenosed.

Levosimendan or dobutamine was started 10 min after induction and continued for 24 h (in the postoperative period). The study drug levosimendan and dobutamine were diluted in such a way that equal infusion rates were achieved for comparable patients. Both the drug syringes were prepared by another person blinded from the study. Syringes and extension tubings were covered to blind the anesthesiologist. Hemodynamic data were noted at 30 min, during OM grafting, 1, 6, 12, and 24 h after shifting to ICU. Heart rate (HR), MAP, pulmonary capillary wedge pressure (PCWP), cardiac index (CI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI), left ventricular stroke work index (LVSWI) and right ventricular stroke work index (RVSWI), mixed venous oximetry (SvO₂), and lactate were measured. Additional inotropes or vasopressors were initiated based on the hemodynamic parameters.

If MAP was more than 55 mmHg, the study drug was continued. If MAP was <55 mmHg with a CI <1.5 L/min/m² and SVRI <1200 units, infusion of noradrenaline at 0.05 µg/kg/min was added in addition to the group inotrope. If MAP was <55 mmHg with a CI <1.5 dyne-s-m²/cm³ and SVRI >1200 units, adrenaline 0.05 µg/kg/min was added in addition to the group inotrope.

As per institutional protocol, tracheal extubation was performed when patients were hemodynamically stable, temperature >36°C, chest tube drainage <1 ml/kg/h, urine output >1 ml/kg/h, and breathing spontaneously with adequate blood gases. Additional inotropes/vasoconstrictors were tapered once the patients were hemodynamically stable.

Statistical analysis

The baseline characteristics between the two groups were compared using Chi-square test for categorical data and the Student’s test for continuous variables. The results are reported as the mean ± standard deviation. Statistical significance was defined as a P < 0.05.

Results

This prospective, randomized, double-blind study included 80 patients with moderate to severe LV dysfunction undergoing OPCAB from September 2012 to January 2014. The mean Euro SCORE for Group I patients was 3.22 ± 1.8 and for Group II patients was 3.13 ± 1.4 (P = 0.36); both groups were comparable in terms of surgical risk stratification.
Table 1 shows the clinical and demographic data of all patients included in the study. The demographic data and comorbid conditions were comparable between the two groups.

Table 2 shows the HR, MAP, PCWP, CI, SVRI, PVRI, LVSWI, and RVSWI at various time intervals. The baseline variables were comparable between the groups.

MAP was <55 mmHg in 16 (40%) patients in the levosimendan group and 9 (22.5%) patients in the dobutamine group, which was managed either with noradrenaline or adrenaline based on the SVRI. In the remaining 55 cases (68.75% of total cases), the MAP was maintained >55 mmHg throughout the study. The reduction in MAP was higher in the levosimendan group compared to the dobutamine group, which was statistically significant at 30 min, during OM grafting, 1, 6, 12 h, and 24 h after surgery. The HR was higher in the dobutamine group, which was statistically significant at 30 min, during OM grafting, 1, 6, 12 h, and 24 h after surgery.

The SVRI was lower in the levosimendan group compared to the dobutamine group, which was statistically significant at 30 min, during OM grafting, 1, 6, 12 h, and 24 h after surgery. Patients who received levosimendan showed a statistically significant decrease in PVRI and PCWP at 30 min, during OM grafting, 1, 6, 12 h, and 24 h after surgery.

The levosimendan group showed statistically significant increase in CI (Figure 1), LVSWI, and RVSWI at 30 min, during OM grafting, 1, 6, 12 h, and 24 h after surgery, compared to the dobutamine group.

Table 3 shows the mean number of grafts and the duration of surgery were comparable between the study groups. Fourteen patients needed noradrenaline infusion in the levosimendan group, whereas only 6 patients needed in dobutamine group, which was statistically significant. Two patients required adrenaline infusion in levosimendan group and 3 patients in dobutamine group. Two patients in the levosimendan group (and one in dobutamine group) required intraoperative ventricular epicardial pacing during RCA anastomosis. Intra-aortic balloon pumping (IABP) was used in one patient in each of the study groups. All patients underwent successful OPCAB without institution of CPB. The incidence of postoperative AF was found to be increased in patients receiving dobutamine (20%) when compared to levosimendan (5%), which was statistically significant. No malignant ventricular arrhythmias were recorded in any patient. One patient required re-exploration for excessive chest drainage in the levosimendan group. The duration of mechanical ventilation, ICU, and hospital stay were lower in the levosimendan group, which was statistically significant.

**Discussion**

This study was designed to evaluate the serial changes of hemodynamic variables and immediate postoperative outcomes in patients with moderate to severe LV dysfunction undergoing OPCAB while using levosimendan or dobutamine as the primary inotrope. The growing need to perform coronary revascularization in patients with severely compromised LV function is the result of increasing number of patients presenting with end-stage ischemic cardiomyopathy. Management of patients with poor LV function caused by coronary artery disease remains a challenge. Surgical intervention by CABG has been regarded as a high-risk procedure. However, recent studies have reported encouraging early, mid and long-term results. 

During OPCAB, frequent heart displacement can cause hemodynamic instability, more significantly in patients with compromised LV function. During handling of the heart, typical changes include an increase in filling pressures (PCWP), which may decrease CI and increases
Table 2: Heart rate, mean arterial pressure, pulmonary capillary wedge pressure, cardiac index, systemic vascular resistance index, pulmonary vascular resistance index, left ventricular stroke work index, and right ventricular stroke work index at various time intervals

| Time       | Group          | HR (beats/min) | MAP (mm Hg) | PCWP (mm Hg) | SVRI (dyne·s·m⁻²) | PVRI (dyne·s·m⁻²) | LVSWI (g/m²·beat) | RVSWI (g/m²·beat) |
|------------|----------------|----------------|-------------|--------------|-------------------|-------------------|-------------------|-------------------|
| Basal      | Levosimendan   | 75.88±4.84     | 87.58±5.77  | 14.68±1.34   | 2555±271.8        | 328.1±32.1        | 36.9±4.36         | 3.66±0.38         |
|            | Dobutamine     | 76.25±3.48     | 87.48±5.69  | 14.05±1.82   | 2503±238.2        | 323.3±27.4        | 36.1±3.87         | 3.57±0.42         |
| 30 min     | Levosimendan   | 79.30±4.42*    | 65.75±4.48* | 10.88±1.24*  | 1900±186.9        | 235.4±28.4*       | 59.8±5.44*        | 6.09±0.38*        |
|            | Dobutamine     | 87.90±3.01     | 80.30±5.02  | 12.93±1.42   | 2965±186.3        | 303.3±24.6        | 48.6±3.41         | 4.61±0.39         |
| OM grafting| Levosimendan   | 78.05±3.67*    | 61.00±3.58* | 12.70±1.06*  | 1911±168.1        | 268.2±20.5*       | 54.6±4.93*        | 5.51±0.37*        |
|            | Dobutamine     | 90.63±3.09     | 72.40±4.52  | 14.73±1.10   | 2294±152.5        | 319.3±28.9        | 41.0±4.38         | 4.08±0.53         |
| 1 h        | Levosimendan   | 79.80±4.26*    | 63.55±3.69* | 10.68±1.26*  | 1727±142.0*       | 207.7±28.7*       | 62.4±4.69*        | 6.27±0.38*        |
|            | Dobutamine     | 92.60±2.92     | 75.95±4.83  | 13.28±1.06   | 1980±117.1        | 259.9±11.3        | 49.9±3.38         | 5.25±0.20         |
| 6 h        | Levosimendan   | 79.97±4.03*    | 64.83±3.24* | 10.63±1.35*  | 1629±125.1*       | 189.9±22.4*       | 64.1±4.75*        | 6.40±0.28*        |
|            | Dobutamine     | 93.70±3.86     | 76.45±4.81  | 13.10±1.27   | 1971±183.0        | 248.6±21.7        | 51.9±5.24         | 5.32±0.16         |
| 12 h       | Levosimendan   | 80.38±4.28*    | 66.85±3.47* | 10.93±1.18*  | 1565±110.4*       | 178.4±16.1*       | 65.2±4.24*        | 6.35±0.28*        |
|            | Dobutamine     | 94.40±3.48     | 76.33±4.72  | 13.35±1.00   | 1902±90.5         | 250.0±15.8        | 50.7±3.99         | 5.29±0.17         |
| 24 h       | Levosimendan   | 81.50±3.89*    | 69.63±3.95* | 11.18±1.03*  | 1537±100.3*       | 170.3±13.4*       | 64.2±2.74*        | 6.45±0.31*        |
|            | Dobutamine     | 95.73±3.48     | 78.58±5.02* | 12.63±1.12   | 1840±104.9        | 250.9±17.1        | 50.0±3.36         | 5.30±0.16         |

Values expressed as mean±SD. *P<0.05. HR: Heart rate (beats/min), MAP: Mean arterial pressure (mm Hg), PCWP: Pulmonary capillary wedge pressure (mmHg), SVRI: Systemic vascular resistance index (dyne·s·m⁻²·cm⁻⁴), PVRI: Pulmonary vascular resistance index (dyne·s·m⁻²·cm⁻⁴), LVSWI: Left ventricular stroke work index (g/m²·beat), RVSWI: Right ventricular stroke work index (g/m²·beat), OM grafting: Values recorded during obtuse marginal grafting, SD: Standard deviation

Figure 1: Cardiac index at various time intervals. Cardiac index (L/min/m²), OM: During obtuse marginal grafting

| Time       | Levosimendan | Dobutamine | P      |
|------------|--------------|------------|--------|
| Basal      | 1.78         | 1.76       | 0.456  |
| 30 min     | 2.76         | 2.00       | <0.001 |
| OM grafting| 2.49         | 1.95       | <0.001 |
| 1 h        | 2.94         | 2.30       | <0.001 |
| 6 h        | 3.01         | 2.29       | <0.001 |
| 12 h       | 3.14         | 2.27       | <0.001 |
| 24 h       | 3.16         | 2.31       | <0.001 |

OM: Obtuse marginal

and arrhythmias and are associated with high mid-term mortality in nonsurgically treated patients with heart failure.

Beta-adrenergic agonists and PDEI, the most commonly used positive inotropic agents, exert a positive inotropic action primarily by increasing cyclic adenosine monophosphate (cAMP) in the cardiac myocytes. Although beta-adrenergic agonists and PDEI are effective positive inotropic agents, their use may be limited by several problems.

The pharmacological effects of levosimendan are as follows: (a) increased cardiac contractility mediated by calcium sensitization of troponin C, (b) vasodilation through the opening of potassium channels on the sarcolemma of smooth muscle cells in the vasculature, (c) cardioprotection through the opening of mitochondrial potassium channels in the cardiomyocytes, and (d) hemodynamics without a significant increase in oxygen consumption has a beneficial effect on neurohormonal levels.

right ventricular end diastolic pressure. Studies have demonstrated contractile dysfunction over the first few hours after myocardial revascularization, which generally resolves spontaneously over 24–48 h. During this period of transient myocardial dysfunction, inotropic agents are usually chosen for hemodynamic support. Traditionally used inotropic agents such as epinephrine, dobutamine, and dopamine are limited by significant increases in myocardial oxygen consumption, proarrhythmias, or neurohormonal activation. Beta-adrenergic agonists and PDEI induce good early hemodynamic values, but favor myocardial ischemia and arrhythmias and are associated with high mid-term mortality in nonsurgically treated patients with heart failure.

Figure 1: Cardiac index at various time intervals. Cardiac index (L/min/m²), OM: During obtuse marginal grafting
Levosimendan has positive inotropic (myocardial relaxation) effects; preserving or improving diastolic properties demonstrated in human clinical studies.[22] We also observed similar effect in the form of decrease in PCWP.

Levosimendan is generally well tolerated. Most of its adverse effects are dose-related and due to its vasodilator effect. In the present study, levosimendan was administered without an initial bolus dose. Administration of a bolus dose often results in profound hypotension due to fall in SVRI, which may not be fully compensated by an increase in CI. It has therefore been suggested that the initial loading dose be reduced or even omitted. In spite of avoiding the bolus dose, 14 out of 40 patients in levosimendan group developed hypotension during OPCAB. As per study protocol, all patients received norepinephrine to maintain a MAP >60 mmHg. Norepinephrine infusion was required in 6 patients in dobutamine group.

For most OPCAB patients, coronary artery anastomosis of left anterior descending (LAD) artery does not cause serious hemodynamic disturbances, but OM artery anastomosis can decrease both right and left ventricle function due to verticalization of the heart (due to atrialization of ventricles and development of magnetic resonance). This is precisely why the hemodynamic data were recorded during OM anastomosis in our study.

There was no significant difference in revascularization (number of grafts) and duration of surgery between the groups in the present study. There was no evidence of tachycardia in levosimendan group why the hemodynamic data were recorded during OM anastomosis in our study.

There was a significant difference between lactate levels (lower in levosimendan group) and SvO₂ levels (higher in levosimendan group) between the two groups. Lactate levels returned to normal (<2 mmol/L) in both the groups [normalization occurred within the first 8 h in levosimendan group and after 8 h in dobutamine group]. Probably, other variables (which have an effect on lactate) such as hypothermia and amount of fluids were involved. There was no significant difference in the requirement of IABP and cardiac pacing between the two groups. None of the patients required conversion to CPB.

In our study, the incidence of postoperative AF was lower in the levosimendan group compared to dobutamine group.[23] This can be partly attributed to its anti-inflammatory and anti-oxidant properties.

### Table 3: Mixed venous oximetry and lactate levels at various time intervals

| Time     | Group        | SvO₂   | Lactate |
|----------|--------------|--------|---------|
| Baseline | Levosimendan | 65.97±4.68 | 1.07±0.10 |
|          | Dobutamine   | 65.10±4.04 | 1.04±0.08 |
| OM grafting | Levosimendan | 63.13±3.39* | 1.93±0.51* |
|          | Dobutamine   | 60.93±4.70 | 2.73±0.52 |
| 1 h      | Levosimendan | 67.80±4.51* | 2.61±0.88* |
|          | Dobutamine   | 63.95±6.62 | 3.53±0.87 |
| 8 h      | Levosimendan | 68.18±4.30 | 1.94±0.61* |
|          | Dobutamine   | 67.30±4.82 | 2.38±0.93 |
| 24 h     | Levosimendan | 68.15±3.71* | 1.12±0.19* |
|          | Dobutamine   | 64.70±6.28 | 1.52±0.37 |

Values expressed as mean±SD. *P<0.05. SvO₂: Mixed venous oximetry (%), lactate (mmol/L), OM: Obtuse marginal, SD: Standard deviation

### Table 4: Comparison of intraoperative and postoperative data

|                  | Levosimendan | Dobutamine | P   |
|------------------|--------------|------------|-----|
| Number of grafts | 3.80±0.405   | 3.78±0.480 | 0.802 |
| Duration of surgery (min) | 231.05±34.4 | 226.75±35.2 | 0.582 |
| Adrenaline (%)   | 2 (5.0)      | 3 (7.5)    | 0.500 |
| Noradrenaline (%)| 14 (35)      | 6 (15)     | 0.035* |
| IABP (%)         | 1 (2.5)      | 1 (2.5)    | 0.753 |
| Pacing (%)       | 2 (5.0)      | 1 (2.5)    | 0.500 |
| Conversion to CPB (%) | 0          | 0          | -   |
| Blood transfusion (%) | 3 (7.5)    | 2 (5.0)    | 0.500 |
| Re-exploration (%) | 1 (2.5)     | 0          | 0.500 |
| Postoperative atrial fribillation (%) | 2 (5.0) | 8 (20.0) | 0.044* |
| Ventilation (h)  | 6.03±1.52    | 7.40±1.90  | 0.001 |
| ICU stay (days)  | 2.85±0.70    | 3.20±0.72  | 0.031* |
| Hospital stay (days) | 5.88±0.60   | 6.85±0.80  | 0.002* |

Values expressed as mean±SD. *P<0.05. IABP: Intra-aortic balloon pumping, CPB: Cardiopulmonary bypass, ICU: Intensive Care Unit, SD: Standard deviation

Levosimendan has shown promise in elective therapy of cardiac surgical patients with high perioperative risk or compromised LV function, as well as in rescue therapy of patients with difficulty in weaning from CPB. Levosimendan and dobutamine both normalized the CI, although the former allowed higher values to be obtained.[13] Levosimendan provokes an early and maintained reduction of the systemic, pulmonary, central venous, and pulmonary capillary blood pressures along with a reduction in the systemic vascular and pulmonary arteriolar resistance.[20]

Our results show that levosimendan significantly increases CI compared with dobutamine, during and after OPCAB. The authors believe that patients overcame transient myocardial dysfunction better with levosimendan by increasing the indices of contractility (CI, LVSWI, RVSWI). Our findings are in agreement with the results observed in recent studies, strengthening the conclusion that the observed increase in CI produced by levosimendan probably results from the combined actions of reduced LV afterload and modest increase in myocardial contractility. However, this is accomplished without increase in cAMP and associated intracellular calcium levels. The result is no increase in myocardial O₂ demand with improved cardiac contractility especially in patients with LV dysfunction.[21] Levosimendan has positive inotropic (myocardial relaxation) effects; preserving or improving diastolic properties demonstrated in human clinical studies.[22] We also observed similar effect in the form of decrease in PCWP.
antioxidant modulation, which are being implicated in the pathogenesis of postoperative AF. Parissis et al. showed that levosimendan caused a significant reduction in interleukin-6 levels in patients with decompensated advanced heart failure compared with placebo.\[24\] Avgeropoulou et al. also showed that a 24-h infusion of levosimendan in contrast to dobutamine decreased malondialdehyde levels, an endproduct of lipid peroxidation, indicating a possible antioxidant effect of levosimendan.\[25\]

Numerous studies have shown significant outcome benefits in terms of shorter ventilation time, shorter ICU, and hospital stay in patients undergoing CABG treated with levosimendan.\[26,27\] In our study, the patients who received levosimendan showed a statistically significant reduction in the duration of ventilation, length of ICU, and hospital stay, compared to the patients who received dobutamine. This can be attributed to its improved myocardial performance profile and partly to the reduced incidence of postoperative arrhythmias.

Our study has few limitations; CI and SVRI were measured only for the first 24 h of the postoperative period, in spite of the effects of levosimendan lasting over a week (due to its active metabolite). The type and amount of intraoperative fluids used were not recorded and renal parameters were not noted. Moreover, intraoperative echocardiographic assessment of myocardial contractility was not performed.

Conclusions

The results of our study indicate that levosimendan is superior to dobutamine in terms of myocardial performance and showed definitive outcome benefits (in terms of reduced incidence of AF and length of ICU and hospital stay) in patients with moderate to severe LV dysfunction undergoing OPCAB.

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Conflicts of interest

There are no conflicts of interest.

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