

Inhaled Levosimendan versus Intravenous Levosimendan in Patients with Pulmonary Hypertension Undergoing Mitral Valve Replacement

Abstract

Context: Inhaled levosimendan may act as selective pulmonary vasodilator and avoid systemic side effects of intravenous levosimendan, which include decrease in systemic vascular resistance (SVR) and systemic hypotension, but with same beneficial effect on pulmonary artery pressure (PAP) and right ventricular (RV) function. **Aim:** The aim of this study was to compare the effect of inhaled levosimendan with intravenous levosimendan in patients with pulmonary hypertension undergoing mitral valve replacement. **Settings and Design:** The present prospective randomized comparative study was conducted in a tertiary care hospital. **Subjects and Methods:** Fifty patients were randomized into two groups ($n = 25$). Group A: Levosimendan infusion was started immediately after coming-off of cardiopulmonary bypass and continued for 24 h at 0.1 mcg/kg/min. Group B: Total dose of levosimendan which would be given through intravenous route over 24 h was calculated and then divided into four equal parts and administered through inhalational route 6th hourly over 24 h. Hemodynamic profile (pulse rate, mean arterial pressure, pulmonary artery systolic pressure [PASP], SVR) and RV function were assessed immediately after shifting, at 1, 8, 24, and 36 h after shifting to recovery. **Statistical Analysis Used:** Intragroup analysis was done using paired student *t*-test, and unpaired student *t*-test was used for analysis between two groups. **Results:** PASP and RV-fractional area change (RV-FAC) were comparable in the two groups at different time intervals. There was a significant reduction in PASP and significant improvement in RV-FAC with both intravenous and inhalational levosimendan. SVR was significantly decreased with intravenous levosimendan, but no significant decrease in SVR was observed with inhalational levosimendan. **Conclusions:** Inhaled levosimendan is a selective pulmonary vasodilator. It causes decrease in PAP and improvement in RV function, without having a significant effect on SVR.

Keywords: Inhalational, intravenous, levosimendan, right ventricular fractional area change, systemic vascular resistance

Introduction

Pulmonary hypertension (PH) is an important cause of morbidity and mortality in patients with cardiac diseases. PH increases right ventricular (RV) work, which can lead to RV dysfunction after cardiopulmonary bypass (CPB). Although the RV has a remarkable ability to compensate for markedly elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), RV failure is the ultimate consequence of severe PH.^[1-3] The presence of RV failure carries a poor prognosis, with high risk of perioperative mortality from 37% to 90%.^[4-6]

For successful management of these patients, drugs to lower PVR should be used. Prostacyclin (PGI₂), phosphodiesterase

inhibitors, such as milrinone and calcium channel sensitizers (levosimendan) have been used successfully for this purpose. However, intravenous administration is limited by systemic hypotension because of nonselective vasodilation and by hypoxemia through worsening of intrapulmonary shunt caused by inhibition of hypoxic pulmonary vasoconstriction.^[7-9]

The above adverse effects warrant the use of selective pulmonary vasodilators, with minimal systemic effects, in patients with PH.

Levosimendan is a pyridazinone dinitrile derivative with positive inotropic, lusitropic, and vasodilatory effects, that have beneficial effects on myocardial performance.^[10] The drug is a calcium-channel sensitizer. Levosimendan improves cardiac contractility without increasing myocardial

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oxygen demand or promoting arrhythmogenesis.^[11] Levosimendan improves the cardiac index^[12] and reduces mortality in patients with preoperative severely reduced LV ejection fraction (EF).^[13] Several studies have shown that levosimendan improves echocardiographic and hemodynamic markers of RV function, when administered to patients with advanced heart failure and compromised RV function since it dilates pulmonary vasculature and improves biventricular function.^[14,15]

There is limited literature available on intravenous levosimendan which has shown a clear benefit during cardiac surgery in patients with severe PH by reducing PAP and decreasing RV afterload.^[9,16-19] Currently, the data for inhaled levosimendan are very scarce.^[20]

In this prospective randomized comparative study, the authors decided to administer levosimendan through two different routes, i.e. through intravenous and inhalational route.

The authors hypothesized that administering levosimendan through inhaled route could avoid the systemic side effects of intravenous levosimendan, which include a decrease in systemic vascular resistance (SVR) and systemic hypotension leading to addition of vasopressors, but with the same beneficial effect on PAP and RV function.

The aim of this study was to compare the effect of inhaled levosimendan with intravenous levosimendan in patients with PH undergoing mitral valve replacement (MVR).

Subjects and Methods

After taking the Institutional Ethics Committee approval, 50 patients were enrolled in this prospective randomized study. Written informed consent was taken from all the patients. We included adult patients with PH undergoing MVR.

We excluded elderly patients above the age of 70 years, patients with a low (EF <35%) and any emergency MVR.

Based on a power analysis from a previous study,^[14] (minimum detectable difference of means = 20%, expected standard deviation (SD) of residuals = 20%, desired power = 80% and an α error = 5%), we determined that a sample size of $n = 20$ would be sufficient to detect a 20% increase in RV-fractional area change (RV-FAC). However, we enrolled 25 patients in each group. Patients were randomized into two groups ($n = 25$) on the basis of computer-generated random table. The groups were as follows:

- Group A – Levosimendan infusion was started immediately after coming off CPB and was continued for 24 h at 0.1 mcg/kg/min
- Group B – Total dose of levosimendan which would be given through intravenous route over 24 h at 0.1 mcg/kg/min was calculated and then divided into four equal parts and administered 6th hourly over 24 h

through a compressor nebulizer (Innovative Medical Devices, New Delhi). The first dose of levosimendan was administered immediately after transferring the patient to the postoperative recovery room.

The inotrope use in all these patients was guided by hemodynamic data such as mean arterial pressure (MAP), central venous pressure along with intraoperative transesophageal echocardiography to maintain a MAP of around 70 mmHg.

A Flotrac monitor was attached to the arterial line to monitor the SVR. Hemodynamic profile (pulse rate [PR], MAP) was obtained before surgery. Pulmonary artery systolic pressure (PASP) and RV function: RV-FAC were assessed through transthoracic echocardiography (TTE) done by an experienced cardiologist. Postsurgery, the patients were shifted to postoperative recovery room. Hemodynamic profile, SVR, PASP, and RV function was assessed immediately after shifting (which was taken as the baseline value for intragroup comparison), at 1, 8, 24, and 36 h after shifting to postoperative recovery room.

The inotropic score (IS) and the vasoactive IS (VIS) in the first 24 h were noted. IS = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 × epinephrine dose (mcg/kg/min).

VIS = IS + (10 × milrinone dose [mcg/kg/min]) + [10,000 × vasopressin dose (units/kg/min)] + (100 × norepinephrine dose [mcg/kg/min]).

The extubation time and postoperative hospital length of stay were also noted.

Statistical analysis was performed using Medcalc software version 12.2.1 (Ostend, Belgium). Patient characteristics were compared using unpaired student *t*-test and Chi-square test. Hemodynamic variables, RV function, and IS values were expressed as mean ± SD. Intragroup analysis was done using paired student *t*-test and unpaired student *t*-test was used for analysis between the two groups. $P < 0.05$ was considered statistically significant.

Results

The patient characteristics were comparable in the two groups [Table 1].

The hemodynamics (PR, MAP) were comparable in the two groups at various time intervals [Table 2a and b].

SVR was significantly decreased with intravenous levosimendan; however, no significant decrease in SVR was observed with inhalational levosimendan [Table 2c].

The PASP and RV-FAC were comparable in the two groups at different time intervals [Table 3a and b]. There was a significant reduction in PASP with both intravenous and inhalational levosimendan at different time

Table 1: Patient characteristics

| | Group A | Group B | P |
|----------------------|------------|-------------|------|
| Age (years) | 40±14.57 | 45±8.88 | 0.15 |
| Gender (male:female) | 18:7 | 15:10 | 0.37 |
| Height (cm) | 157±9.28 | 161±9.68 | 0.14 |
| Weight (kg) | 55.43±8.93 | 54.49±14.09 | 0.78 |

Table 2a: Comparison of pulse rate (beats/min) between the study groups at different time intervals

| | Group A | Group B | P |
|-------------------------|------------|------------|------|
| Preoperative | 95.6±8.22 | 91.1±18.75 | 0.28 |
| Immediate postoperative | 84.5±10.95 | 81.8±16.90 | 0.51 |
| 1 h postoperative | 87.1±12.24 | 87.7±18.24 | 0.89 |
| 8 h postoperative | 88.4±11.94 | 88.2±18.46 | 0.96 |
| 24 h postoperative | 87.6±12.97 | 88.1±18.91 | 0.91 |
| 36 h postoperative | 84.7±9.32 | 88.8±18.74 | 0.33 |

Table 2b: Comparison of mean arterial pressure (mmHg) between the study groups at different time intervals

| | Group A | Group B | P |
|-------------------------|-----------|------------|------|
| Preoperative | 79.7±6.17 | 83.4±11.67 | 0.17 |
| Immediate postoperative | 72.3±8.82 | 76.5±10.16 | 0.13 |
| 1 h postoperative | 72.7±8.81 | 77.2±10.37 | 0.10 |
| 8 h postoperative | 75.0±6.43 | 78.0±10.50 | 0.23 |
| 24 h postoperative | 75.3±5.94 | 77.2±13.42 | 0.52 |
| 36 h postoperative | 78.5±5.02 | 77.3±10.89 | 0.62 |

intervals [Table 4a and b]. There was also a significant improvement in RV-FAC with both intravenous and inhalational levosimendan at different time intervals [Table 4a and b].

The IS and VIS in the first 24 h were significantly higher in the intravenous levosimendan group as compared to the inhalational levosimendan group [Table 5].

The postoperative ventilator hours and the postoperative hospital length of stay were comparable in the two groups [Table 5].

Discussion

PH has been recognized as a known risk factor for poor outcome in patients undergoing MVR. The mortality rate of MVR in such patients has been reported up to 31%.^[21,22] For successful management, it is essential to lower PVR and PAP in these patients, with minimal effect on systemic vasculature.

The major findings of the present study were that inhaled levosimendan causes a decrease in PAP and an improvement in the RV function in a similar manner as intravenous levosimendan [Table 3a and b]. However, while inhaled levosimendan did not have a significant effect on the SVR, intravenous levosimendan decreased

Table 2c: Comparison of systemic vascular resistance (dynes.s/cm⁵) between the study groups at different time intervals

| | Group A | Group B | P |
|-------------------------|----------------|----------------|---------|
| Preoperative | 1325.4±235.39 | 1292.65±221.84 | 0.62 |
| Immediate postoperative | 1095.45±130.17 | 1083.4±105.59 | 0.72 |
| 1 h postoperative | 885.11±169.02 | 1061.1±87.67 | <0.0001 |
| 8 h postoperative | 851±140.92 | 1070.33±78.78 | <0.0001 |
| 24 h postoperative | 957.64±55.16 | 1055.9±56.54 | <0.0001 |
| 36 h postoperative | 1060.73±87.93 | 1044.95±68.69 | 0.48 |

Table 3a: Comparison of pulmonary artery systolic pressure (mmHg) between the study groups at different time intervals

| | Group A | Group B | P |
|-------------------------|------------|-------------|------|
| Preoperative | 77±9.62 | 76.35±18.07 | 0.87 |
| Immediate postoperative | 48.24±5.85 | 45.48±5.97 | 0.11 |
| 1 h postoperative | 41.76±3.8 | 40.76±4.42 | 0.40 |
| 8 h postoperative | 41.6±3.83 | 40.6±4.56 | 0.41 |
| 24 h postoperative | 36.8±2.83 | 35.4±4.47 | 0.19 |
| 36 h postoperative | 34.68±2.5 | 35.08±4.73 | 0.71 |

Table 3b: Comparison of the right ventricular-fractional area change (%) between the study groups at different time intervals

| | Group A | Group B | P |
|-------------------------|------------|------------|------|
| Preoperative | 25.9±4.84 | 27.85±4.25 | 0.14 |
| Immediate postoperative | 33.12±4.28 | 33±3.35 | 0.91 |
| 1 h postoperative | 37.04±4.09 | 36.84±3.09 | 0.85 |
| 8 h postoperative | 37.64±4.32 | 38.64±1.96 | 0.30 |
| 24 h postoperative | 41.08±4.13 | 40.12±2.13 | 0.31 |
| 36 h postoperative | 41.24±4.06 | 40.76±2.39 | 0.61 |

the SVR significantly [Table 2c]. This suggests that inhaled levosimendan has a selective pulmonary vasodilatory action as compared to intravenous levosimendan. As a consequence of the above, the IS and VIS in the first 24 h were significantly lower in the inhaled levosimendan group as compared to the intravenous levosimendan group [Table 5]. The VIS includes use of vasopressors such as noradrenaline and vasopressin. The authors predict that the decrease in SVR in intravenous levosimendan group could have been negated substantially by the use of above vasopressors and when levosimendan is used alone, the SVR could have been decreased to a greater extent. Despite the use of vasopressors, when SVR was compared between intravenous and inhaled levosimendan groups, it showed a statistically significant decrease in intravenous levosimendan group.

The postoperative ventilator hours and the postoperative hospital length of stay were comparable in the two groups [Table 5].

Table 4a: Comparison of pulmonary artery systolic pressure (mmHg) and right ventricular-fractional area change (%) with the baseline at different time intervals in Group A

| | Baseline | 1 h | P | 8 h | P | 24 h | P | 36 h | P |
|--------|------------|------------|---------|------------|---------|------------|---------|------------|---------|
| PASP | 48.24±5.85 | 41.76±3.8 | <0.0001 | 41.6±3.83 | <0.0001 | 36.8±2.83 | <0.0001 | 34.68±2.5 | <0.0001 |
| RV-FAC | 33.12±4.28 | 37.04±4.09 | <0.0001 | 37.64±4.32 | <0.0001 | 41.08±4.13 | <0.0001 | 41.24±4.06 | <0.0001 |

PASP: Pulmonary artery systolic pressure, RV-FAC: Right ventricular-fractional area change

Table 4b: Comparison of pulmonary artery systolic pressure (mmHg) and right ventricular-fractional area change (%) with the baseline at different time intervals in Group B

| | Baseline | 1 h | P | 8 h | P | 24 h | P | 36 h | P |
|--------|------------|------------|---------|------------|---------|------------|---------|------------|---------|
| PASP | 45.48±5.97 | 40.76±4.42 | <0.0001 | 40.6±4.56 | <0.0001 | 35.4±4.47 | <0.0001 | 35.08±4.73 | <0.0001 |
| RV-FAC | 33±3.35 | 36.84±3.09 | <0.0001 | 38.64±1.96 | <0.0001 | 40.12±2.13 | <0.0001 | 40.76±2.39 | <0.0001 |

PASP: Pulmonary artery systolic pressure, RV-FAC: Right ventricular-fractional area change

Table 5: Comparison of inotropic score in first 24 h, vasoactive-inotropic score in first 24 h, postoperative ventilatory hours and postoperative hospital length of stay (days) between the study groups

| | Group A | Group B | P |
|---|-----------|-----------|--------|
| Inotropic score in first 24 h (excluding levosimendan) | 6.04±3.55 | 4.25±1.39 | 0.02 |
| Vasoactive-inotropic score in first 24 h (excluding levosimendan) | 7.68±4.35 | 4.25±1.39 | 0.0005 |
| Postoperative ventilatory hours | 6.83±2.56 | 6.25±1.28 | 0.32 |
| Postoperative hospital length of stay | 6.77±1.07 | 7.05±2.24 | 0.58 |

The dose of inhaled levosimendan administered was the same as administered through the intravenous route in 24 h. TTE was done at regular intervals to assess the effect of the drug on PASP and RV-FAC. Consequently, a FloTrac monitor was used to monitor the SVR in the two groups.

There is limited literature, where inhaled levosimendan has been used to lower PAP and improve the RV function in patients with PH. Prophylactic inhalation of levosimendan has been shown to improve survival and reduce the release of inflammatory mediators in an experimental model of ventilator-induced lung injury in rats.^[20]

In the present study, the decrease in PASP by inhaled levosimendan was comparable to intravenous levosimendan. Similarly, the improvement in RV-FAC caused by inhaled levosimendan was comparable to intravenous levosimendan. This suggests that inhaled levosimendan is as effective as intravenous levosimendan in reducing the PASP and improving the RV function.

Amor *et al.*^[19] reported that intravenous levosimendan decreased PVR and PAPs significantly. Russ *et al.*^[15] also observed that a 24h infusion of levosimendan in patients with cardiogenic shock following acute myocardial infarction resulted in beneficial hemodynamic effects. These included a decrease in PVR and an increase in cardiac

index. The authors did not measure PVR in the present study because that would have necessitated the insertion of a pulmonary artery catheter in all patients. However, we recorded the PASP with TTE at different time intervals in both the groups. There was a significant decrease in PASP in both the groups as compared to the baseline values.

In the present study, there was an improvement in RV-FAC in both the groups at different time intervals. The results of the present study are in agreement with the study conducted by Morelli *et al.*^[23] where they showed an increase in RV function parameters after 24 h of levosimendan infusion in pressure-overloaded RV in patients with acute respiratory distress syndrome. Russ *et al.*^[15] also showed that levosimendan infusion improved hemodynamic parameters of RV performance when used in cardiogenic shock following acute myocardial infarction. In another study conducted by Tewari *et al.*,^[24] the authors noticed significant improvement in the echo RV parameters of tricuspid annular plane systolic excursion (TAPSE), FAC and S' velocity in the levosimendan group. However, TAPSE was not done in the current study because many patients underwent tricuspid valve annuloplasty.

In a recent study, Mishra *et al.*^[9] compared the effects of intravenous levosimendan and intravenous milrinone in cardiac surgery patients with PH and left ventricular dysfunction. The major side effect of using intravenous levosimendan was a fall in SVR, leading to systemic hypotension. Similarly, Amor *et al.*^[19] reported a significant decrease in SVR and MAP with intravenous levosimendan. Similar results were seen in the present study, in which there was a significant decrease in SVR with the use of intravenous levosimendan. However, decrease in SVR was not observed with inhalational levosimendan.

We calculated the IS and VIS in both the groups over 24 h and found that intravenous levosimendan was associated with a significantly higher IS and VIS as compared to inhaled levosimendan. This suggests greater use of vasopressors in intravenous levosimendan group, as compared to inhaled levosimendan group to increase the SVR and maintain the MAP. Still there was a statistically significant difference in SVR between the two groups.

This could be a major clinical advantage of using inhaled levosimendan over intravenous levosimendan.

The postoperative ventilator hours and postoperative hospital length of stay were comparable between the two groups.

Conclusions

The authors conclude that administering levosimendan through different route could avoid the adverse effects of the drug. There is no statistical significant decrease in SVR and no additional requirement of vasopressors in the inhaled levosimendan group, although the decrease in PASP and improvement in RV-FAC is similar to intravenous levosimendan.

Hence, the authors suggest the use of levosimendan by changing the route of administration of the drug to decrease PAP and improve RV function in patients who are hypovolemic with borderline MAP.

One of the limitations of the study was that PASP was assessed using TTE. It would have been more reliable to insert a pulmonary artery catheter for measuring PASP. However, due to economic constraints, we had to go with the next best option of estimating PASP using transthoracic echocardiography. Another limitation of the present study was that the onset of action as well as the duration of action of inhaled levosimendan was not investigated. Further studies are needed to know the onset and duration of action of levosimendan through the inhalational route.

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Conflicts of interest

There are no conflicts of interest.

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