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Original Article

Study of the hemodynamic effect of inhaled milrinone versus inhaled nitroglycerin on mechanically ventilated patients with pulmonary hypertension after mitral valve replacement surgeries

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Abstract

Introduction

Pulmonary arterial hypertension (PH) is commonly found in patients with mitral valve diseases. Most of the drugs used for PH treatment are nonselective pulmonary vasodilators that may cause a modest decrease in pulmonary arterial pressure, but they may cause a marked decrease in systemic vascular resistance as well, which leads to hypotension and a decrease in perfusion of vital organs. Inhaled drugs such as milrinone and nitroglycerine may be safer as a large dose of the drug can selectively target the pulmonary circulation, which leads to a reduction of their systemic adverse effects.

Aim

This double-blind, randomized study compared milrinone inhalation versus nitroglycerin inhalation on pulmonary artery pressure and other hemodynamics in postoperative patients immediately after mitral valve replacement surgery.

Patients and methods

A total of 40 participants with isolated mitral stenosis or isolated mitral incompetence or their combination plus PH [mean pulmonary artery pressure (mPAP) >40 mmHg] scheduled for mitral valve replacement were interviewed. Immediately postoperatively in the ICU, we randomized the patients into two groups, with 20 patients each. Group A consisted of 20 patients who received milrinone inhalation, whereas group B consisted of 20 patients who received nitroglycerine inhalation. Hemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, central venous pressure, pulmonary artery systolic pressure, pulmonary diastolic pressure, mPAP, fractional shortening, ejection fraction, and pressure of oxygen/fraction of inspired oxygen ratio) were recorded in both groups at three time points: T1, before drug delivery; T2, just after drug delivery; and T3, just before extubation.

Results

The study showed that both milrinone and nitroglycerin inhalation caused a marked reduction in systolic, diastolic, and mPAPs without causing any hemodynamic deterioration effects on systolic, diastolic, or mean arterial pressures.

Conclusion

Although both milrinone and nitroglycerin inhalation proved to be effective pulmonary artery vasodilators that avoided systemic adverse effects, nitroglycerin inhalation is a less expensive, easily obtained drug that can serve as an inhaled pulmonary vasodilator in patients with mitral valve diseases and PH following mitral valve replacement surgeries.

Keywords: Milrinone inhalation, mitral valve replacement, mitral valve surgery, nitroglycerine inhalation, pulmonary hypertension

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Introduction

Pulmonary arterial hypertension (PH) is an aggressive, highly fatal disease. Treatment of PH have shown many new modalities in the past 10 years [1]. Although there are many new drugs for the management of PH, the mortality rate remains very high [2].

PH is prevalent in patients with mitral valve disease, especially those who have long-standing severe mitral valve diseases requiring mitral valve replacement surgeries.

Systemic administration of pulmonary artery vasodilator drugs may cause a modest reduction in pulmonary arterial pressure, but they may decrease the systemic vascular resistance, causing hypotension and hypoperfusion of the vital organs; this raised the idea of using nonselective pulmonary artery vasodilators like milrinone by inhalation targeting the pulmonary vascular bed, aiming to avoid the systemic adverse effects of systemic administration [3]. Patients with severe mitral valve diseases usually have concomitant PH. In these patients, treating PH is crucial to avoid the most serious complication, which is right ventricular failure. To avoid the systemic adverse effects of intravenous drug administration, some trials have shown the efficacy of administering some drugs by inhalation to target the pulmonary blood vessels directly to decrease pulmonary arterial pressure such as nitric oxide [4].

Administration of intravenous pulmonary vasodilators such as nitroglycerine and prostaglandins may cause systemic adverse effects; on the contrary, inhalation of these drugs may be more beneficial as this inhalation route only targets the pulmonary vessels avoiding the systemic adverse effects.

Some studies have shown that nitroglycerine inhalation is effective in decreasing the pulmonary artery pressure in patients with PH undergoing mitral valve replacement surgeries [5].

Aim

This double-blind, randomized study compared milrinone versus nitroglycerin when administered by inhalation on pulmonary artery pressure and other hemodynamics in postoperative patients immediately after mitral valve replacement surgery.

Patients and methods

This study is a prospective double-blinded randomized clinical trial. It was performed after approval of the Research Ethics Committee. Patients with isolated mitral stenosis or isolated incompetence or their combination plus PH [mean pulmonary artery pressure (mPAP) >40 mmHg] scheduled for mitral valve replacement were interviewed. The study was discussed with all patients, and a written informed consent was obtained. This research included 40 patients. Patients were randomized into two groups (20 patients each).

Inclusion criteria

The following were the inclusion criteria:

(1) The age ranged from 18 to 65 years old.
(2) Patients with preoperative mitral valve disease (isolated mitral stenosis, regurgitation, or combined stenosis and regurgitation) with PH (mPAP >40 mmHg) were admitted to postoperative ICU after elective mitral valve replacement surgery.
(3) Both sexes.
(4) Left ventricular ejection fraction (LVEF) over 40%.

Exclusion criteria

The following were the exclusion criteria:

(1) Patients undergoing emergency surgery.
(2) Redo surgeries.
(3) History of chronic obstructive lung disease, severe chronic kidney disease, liver dysfunction, coagulopathy, or thrombocytopenia.

The sample size was calculated using Power Analysis and Sample Size 11 (PASS11, NCSS Utah, USA) program.

Methodology

On receiving the patient in the cardiothoracic ICU, patients were randomized into two groups: group A (inhaled milrinone) and group B (inhaled nitroglycerine). All patients were mechanically ventilated with a Drager Evita V300 ventilator. In all patients, we used volume-cycled ventilation. Tidal volume was calculated according to the body weight of 8 ml/kg and inspiratory/expiratory ratio of 1: 2. The respiratory rate was 12 breaths/min, and then the ventilation settings were adjusted to obtain an end-tidal carbon dioxide of 30–40 mmHg. Patients were sedated with propofol infusion 50–100 μg/kg/min or the combination of fentanyl (0.1 μg/kg/min) and propofol (25–50 μg/kg/min). Prefilled syringes containing either milrinone or nitroglycerin (according to the patient's body weight) were prepared and sent by the hospital pharmacy to the postoperative ICU to be nebulized. The patient, the performer of the transthoracic echocardiographer, the intensivist, and the nurse collecting data were blinded to the drug given.

Inhaler administration protocol

In group A, patients received inhaled milrinone (50 μg/kg) diluted to 5 ml in normal saline over a 15-min period through a nebulizer [one side connected to the inspiratory port of the ventilator circuit just proximal to the endotracheal tube (10–20 cm) and the other side connected to nebulization port of the ventilator] immediately after transferring patients to the ICU. In group B, patients received inhaled nitroglycerine (50 μg/kg) diluted to 5 ml in normal saline over a 15-min period in the same way as group A.

Data collection

Hemodynamic parameters were measured clinically, other echo-derived data were measured, and then all data were recorded. The data recorded were heart rate (HR);

systolic, diastolic, and mean arterial blood pressure (MBP; mmHg); central venous pressure (CVP) (mmHg); systolic, diastolic, and mPAP (mmHg); EF%; and fractional shortening (FS%) using transthoracic two-dimensional echocardiography (ACUSON X Ultrasound System; Siemens, Germany). All of the transthoracic echocardiography studies were performed by the same investigator who was an expert in performing transthoracic two-dimensional echocardiography.

To obtain the systolic pulmonary artery pressure (SPAP), in the apical four-chamber view, tracing of the tricuspid valve regurgitant jet with color Doppler was done, followed by application of continuous-wave Doppler to the regurgitant jet to measure the tricuspid regurge jet velocity (TR V), and then the pressure difference between the right atrium and the right ventricle using the modified Bernoulli equation was calculated, which states that the pressure difference equals four multiplied by the velocity square delta (P) = 4 × [TR Vmax] 2. Then, to obtain the PASP, we added the pressure difference (P) to the right atrial pressure (RAP), which is calculated by measuring the inferior vena cava diameter and collapsibility index in the subcostal view. Calculation of the SPAP was done using the equation (SPAP = 4 × (TR Vmax) 2 + RAP); this echo method is an accurate noninvasive method that correlates well with the gold standard method, which is the right-side heart catheterization [6].

To obtain the pulmonary artery diastolic pressure (PADP), tracing of pulmonic valve regurgitation (PR) with color wave Doppler was performed in the short-axis parasternal view, and then application of continuous wave (Doppler at a sweep speed of 100 mm/s was done to measure the peak PR velocity. The peak pressure difference between the pulmonary artery and the right ventricle (measured by the modified Bernoulli equation) was then added to the RAP. PADP was calculated from the formula (PADP = 4 × (PR Vmax) 2 + RAP). This echo method is an accurate noninvasive method that correlates well with the gold standard method, which is right-side heart catheterization. mPAP can be calculated from the following formula: mPAP = 2/3 (PADP)+1/3 (PASP) [6].

To obtain EF and FS, LV function was evaluated using the 4-chamber view and parasternal short-axis view. Arterial and central venous blood samples have been obtained during each assessment point and immediately analyzed, and arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2) ratio has been calculated by standard formulas. Hemodynamic parameters have been measured on arrival from the operating room (T1), immediately after the end of inhalation (T2), and just before extubation (T3).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22.0. Quantitative data were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage.

Results

Demographics

The two groups were similar regarding sex and age (Table 1).

Data collection

Hemodynamic parameters were collected in both groups at three time points: T1, before drug inhalation; T2, just after drug inhalation; and T3, just before extubation. The data were recorded and tabulated (Table 2).

Before drug delivery (T1)

Data of the two groups were compared before drug delivery, including HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), MBP, SPAP, diastolic pulmonary artery pressure (DPAP), mPAP, CVP, LVEF, FS, and the ratio of PaO_2/FiO_2 ratio, and there were no statistically significant differences between the two groups ($P > 0.05$) (Table 3).

After delivery of the drugs (T2)

Data of the two groups were compared after drug delivery, including HR, SBP, DBP, MBP, SPAP, DPAP, mPAP, CVP, LVEF, FS, and PaO_2/FiO_2 ratio, and there were no statistically significant differences between groups ($P > 0.05$) (Table 4).

Just before extubation (T3)

Data of the two groups were compared just before extubation, including HR, SBP, DBP, MBP, SPAP, DPAP, mPAP, CVP, LVEF, FS, and PaO_2/FiO_2 ratio, and there were no statistically significant differences between groups ($P > 0.05$) (Table 5).

Milrinone group

Data were compared in the milrinone group between T1 and T2 to compare the effects of the drug before and after delivery and between T1 and T3 (before delivery and before extubation) to compare the extended effect of the drug. We recorded HR, SBP, DBP, MBP, SPAP, DPAP, mPAP, CVP, LVEF, FS, and PaO_2/FiO_2, and there was no statistically significant difference in hemodynamic parameters in the milrinone group at the three measuring points (T1, T2, and T3) ($P > 0.05$) except for SPAP, DPAP, mPAP, and PaO_2/FiO_2 ratio between T1 and T2 ($P < 0.001$) (Tables 6 and 7 and Fig. 1).

Nitroglycerine group

Data were compared in the nitroglycerin group between T1 and T2 to compare the parameters before and after drug delivery and between T1 and T3 (before delivery and before extubation) to compare the extended effect of the drug. The following hemodynamic data were recorded: HR, SBP, DBP, MBP, SPAP, DPAP, mPAP, CVP, LVEF, FS, and PaO_2/FiO_2. There were no statistically significant differences in hemodynamic parameters in the nitroglycerine group at the three measuring

Table 1: Demographic data of the two study groups

	Milrinone group ($n=20$)	Nitroglycerin group ($n=20$)	t	P
Age (years)	44.3±11.2	45.55±12.39	0.34	0.74
Sex (M/F)	12/8	10/10	$\chi^2=0.1$	0.751

Data are expressed as mean±SD. t, Student t test; χ^2, χ^2 test.

Table 2: Data of both milrinone and nitroglycerin groups before delivery of the drug T1, just after drug delivery T2, and before extubation T3

	Before drug delivery (T1)		After drug delivery (T2)		Just before extubation (T3)	
	Milrinone group	Nitroglycerin group	Milrinone group	Nitroglycerin group	Milrinone group	Nitroglycerin group
HR	106.55±31.83	102.25±32.78	100.4±10.95	96.45±9.16	98.15±12.9	93.05±11.6
SBP	128.85±27.84	128.9±29.72	132.7±25.45	133.2±22.73	133.85±23.5	132.7±23.57
DBP	71.35±10.6	67.9±10.39	75.4±15.13	73.45±14.31	75.15±13.03	70.95±9.23
MBP	90.52±14.84	89.48±14.42	90.28±14.33	91.87±18.85	93.57±16.16	94.72±12.64
SPAP	60.75±8.76	60.3±8.6	48.05±7.95*	52.85±9.71*	60.1±8.045	60.2±9
DPAP	34.05±5.75	34.05±5.67	25.65±4.68*	27.53±6.61*	32.4±8.16	33.65±5.28
mPAP	42.95±5.77	42.8±5.42	33.12±5.01*	35.97±5.93*	41.63±7.57	42.5±5.39
CVP	8.6±2.6	8.6±1.57	9.7±2.74	9.05±2.74	9.5±2.2	9.5±1.7
LVEF	43.1±7.37	44.1±10.26	45.8±7.9	42.3±7.3	45.65±5.72	43.35±5.19
FS	23.1±3.85	21.8±5.26	23.3±3.71	21.1±3.74	23.5±3.4	21.95±2.37
PaO_2/FiO_2 ratio	260.25±43.47	261.25±43.48	275.2±41.25*	274.15±41.21*	251.85±47.3	259.8±47.02

CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FS, fractional shortening; HR, heart rate; LVEF, left ventricular ejection fraction; MBP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PaO_2/FiO_2, pressure of oxygen/fraction of inspired oxygen ratio; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure. *Significant compared with T1 reading in the same group.

Table 3: Data of the two study groups before drug delivery (T1)

	Milrinone group (*n*=20)	Nitroglycerin group (n=20)	*t*	*P*
HR	106.55±31.83	102.25±32.78	0.421	0.676
SBP	128.85±27.84	128.9±29.72	0.01	0.996
DBP	71.35±10.6	67.9±10.39	1.04	0.305
MBP	90.52±14.84	89.48±14.42	0.223	0.824
SPAP	60.75±8.76	60.3±8.6	0.16	0.871
DPAP	34.05±5.75	34.05±5.67	0.00	1
mPAP	42.95±5.77	42.8±5.42	0.085	0.933
CVP	8.6±2.6	8.6±1.57	0.0	1
LVEF	43.1±7.37	44.1±10.26	0.35	0.73
FS	23.1±3.85	21.8±5.26	0.89	0.378
PaO_2/FiO_2 ratio	260.25±43.47	261.25±43.48	0.07	0.94

Data are expressed as mean±SD. CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FS, fractional shortening; HR, heart rate; LVEF, left ventricular ejection fraction; MBP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PaO_2/FiO_2, pressure of oxygen/fraction of inspired oxygen ratio; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; *t*, Student *t* test.

points (T1, T2, and T3) ($P > 0.05$), except for SPAP, DPAP, and mPAP between T1 and T2 ($P < 0.001$) and PaO_2/FiO_2 ratio between T1 and T2 ($P = 0.002$) (Tables 8 and 9 and Fig. 2).

There were no statistically significant differences between the two studied groups concerning hemodynamic variables at the three measuring points [before drug delivery (T1), after drug delivery (T2), and just before extubation (T3)]. This means that in both groups, neither milrinone nor nitroglycerine inhalation caused any significant hemodynamic change regarding SBP, DBP, MBP, CVP, HR, EF, and FS.

Although nitroglycerine inhalation at T2 succeeded to significantly decrease SPAP, DPAP, and mPA*P* values compared with the readings before drug delivery T1, milrinone

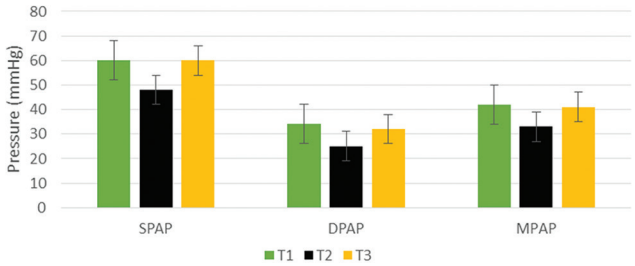

Figure 1: Systolic pulmonary pressure (SPAP), diastolic pulmonary pressure (DPAP), and mean pulmonary artery pressure (mPAP) of the milrinone group before delivery of the drug (T1), after delivery of the drug (T2), and before extubation (T3). Error bar represents SD.

inhalation produced a statistically significant decrease in the same measured variables SPAP, DPAP, and mPAP.

This means that both drugs caused a significant decrease in SPAP, DPAP, and mPAP after inhalation, with no significant differences between milrinone and nitroglycerine groups. PaO_2/FiO_2 ratio showed a statistically significant increase in the two studied groups after drug administration. When T2 values were compared with T1 values, no statistically significant differences were noted between groups. Values of SPAP, DPAP, mPAP, and PaO_2/FiO_2 ratio returned to values measured before drug delivery, with no differences when compared with T1 recorded results.

Discussion

PH is a frequent complication associated with severe mitral valve diseases. It may affect the right ventricle causing right ventricular failure due to pressure overload and may increase the risk of death in severe cases [7].

There are several medications that are currently used to decrease the pulmonary artery pressure in patients with PH. These drugs

Table 4: Data of the two study groups after delivery of the drugs (T2)

	Milrinone group (*n*=20)	Nitroglycerin group (*n*=20)	*t*	*P*
HR	100.4±10.95	96.45±9.16	1.23	0.224
SBP	132.7±25.45	133.2±22.73	0.066	0.948
DBP	75.4±15.13	73.45±14.31	0.419	0.678
MBP	90.28±14.33	91.87±18.85	0.299	0.767
SPAP	48.05±7.95	52.85±9.71	1.7	0.096
DPAP	25.65±4.68	27.53±6.61	1.04	0.308
mPAP	33.12±5.01	35.97±5.93	1.64	0.109
CVP	9.7±2.74	9.05±2.74	0.75	0.458
LVEF	45.8±7.9	42.3±7.3	1.46	0.15
FS	23.3±3.71	21.1±3.74	1.87	0.07
PaO_2/FiO_2 ratio	275.2±41.25	274.15±41.21	0.08	0.936

Data are expressed as mean±SD. CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FS, fractional shortening; HR, heart rate; LVEF, left ventricular ejection fraction; MBP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PaO_2/FiO_2, pressure of oxygen/fraction of inspired oxygen ratio; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; *t*, Student *t* test.

Table 5: Data of the two study groups just before extubation (T3)

	Milrinone group (*n*=20)	Nitroglycerin group (*n*=20)	*t*	*P*
HR	98.15±12.9	93.05±11.6	1.32	0.197
SBP	133.85±23.5	132.7±23.57	0.15	0.878
DBP	75.15±13.03	70.95±9.23	1.18	0.25
MBP	93.57±16.16	94.72±12.64	0.251	0.804
SPAP	60.1±8.045	60.2±9	0.037	0.971
DPAP	32.4±8.16	33.65±5.28	0.57	0.57
mPAP	41.63±7.57	42.5±5.39	0.417	0.679
CVP	9.5±2.2	9.5±1.7	0.0	1
LVEF	45.65±5.72	43.35±5.19	1.33	0.19
FS	23.5±3.4	21.95±2.37	1.67	0.103
PaO_2/FiO_2 ratio	251.85±47.3	259.8±47.02	0.533	0.597

Data are expressed as mean±SD. CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FS, fractional shortening; HR, heart rate; LVEF, left ventricular ejection fraction; MBP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PaO_2/FiO_2, pressure of oxygen/fraction of inspired oxygen ratio; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; *t*, Student *t* test.

include intravenous vasodilators (such as nitrates, milrinone, or prostaglandins); they can decrease pulmonary artery pressure but may cause systemic adverse effects as they decrease peripheral vascular resistance, which may result in hypotension when higher doses are used owing to lack of pulmonary selectivity. This may be an obstacle preventing their use [8].

Systemic use of both nitroglycerin and milrinone by intravenous infusion is used to treat PH; however, they may cause a marked decrease in the systemic blood pressure as well. Nitroglycerin inhalation has shown safety in the treatment of PH as it has no adverse effects [4].

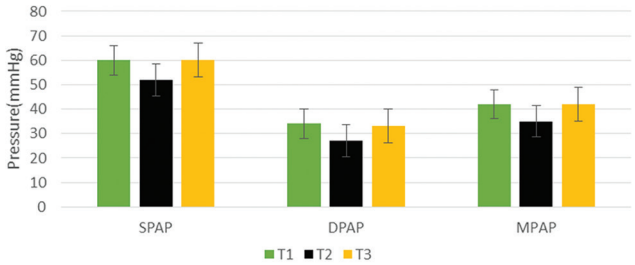

Figure 2: Systolic pulmonary pressure (SPAP), diastolic pulmonary pressure (DPAP), and mean pulmonary artery pressure (mPAP) of nitroglycerin group before delivery of the drug (T1), after delivery of the drug (T2), and before extubation (T3). The error bar represents the SD.

Targeting the pulmonary circulation by drugs that are administered by inhalation can cause a marked reduction in the pulmonary artery pressure avoiding the systemic adverse effects [8]. The Food and Drug Administration approved two drugs to be used as inhaled pulmonary vasodilators; they are inhaled nitric oxide and inhaled prostacyclin analogs [4].

Nitric oxide inhalation causes selective pulmonary vasodilatation avoiding the systemic decrease in peripheral arterial resistance that causes hypotension [9].

Milrinone inhalation has been studied in postoperative patients after heart surgery. Inhalation route has fewer effects on systemic vascular resistance and the MBP compared with systemic administration, but both have similar effects on pulmonary arterial pressure, PVR, and cardiac output [10].

In the current study, we compared milrinone versus nitroglycerin inhalation in the treatment of PH in patients with mitral valve diseases in the early postoperative period. Our results demonstrated that inhalation of both milrinone and nitroglycerin after mitral valve replacement surgery produces significant reductions in mPAP, SPAP, and DPAP without affecting MBP, systolic arterial pressure, diastolic arterial pressure, and HR. The reduction in mPAP was statistically significant ($P < 0.05$).

One of the early studies that described the effect of inhaled milrinone on pulmonary artery pressure was published in the year 2001 by Haraldsson and colleagues. The study was open labeled that was carried out on 20 patients after cardiac surgery in the ICU. The trial was done in two parts, where the first part included nine patients, and there was a marked reduction in the mPAP with an increasing dose of milrinone without a significant change in other hemodynamic parameters such as HR, MBP, and CVP during inhalation of milrinone, and this is in accordance with our study. After 20 min of termination of milrinone inhalation, all the measured variables returned to their baseline [11]. No patient presented systemic hypotension, which is similar to our observation.

In a study by Sablotzki and Starzmann, 18 patients candidates of heart transplantation were given inhaled milrinone. The mPAP decreased only in patients with PH with mean pulmonary pressure above 30 mmHg. Cardiac output increased, with no systemic hypotension [12].

Table 6: Data of milrinone group before and after delivery of the drug

	T1 (n=20)	T2 (n=20)	t	P
HR	106.55±31.83	100.4±10.95	0.96	0.35
SBP	128.85±27.84	132.7±25.45	0.456	0.653
DBP	71.35±10.6	75.4±15.13	1.046	0.309
MBP	90.52±14.0.84	90.28±14.33	0.07	0.95
SPAP	60.75±8.77	48.05±7.95	7.87	<0.001
DPAP	34.05±5.75	25.65±4.68	6.2	<0.001
mPAP	42.95±5.77	33.12±5.01	10.25	<0.001
CVP	8.6±2.6	9.7±2.7	1.56	0.136
LVEF	43.1±7.37	45.8±7.9	1.68	0.109
FS	23.1±3.85	23.3±3.71	0.295	0.772
PaO_2/FiO_2 ratio	260.25±43.478	275.2±41.25	4.132	<0.001

Data are expressed as mean±SD. CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FS, fractional shortening; HR, heart rate; LVEF, left ventricular ejection fraction; MBP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PaO_2/FiO_2, pressure of oxygen/fraction of inspired oxygen ratio; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; *t*, paired *t* test.

Table 7: Data of milrinone group before delivery of the drug T1 and before extubation T3

	T1 (n=20)	T3 (n=20)	t	P
HR	106.55±31.83	98.15±12.89	1.29	0.212
SBP	128.85±27.84	133.85±23.53	1.32	0.203
DBP	71.35±10.6	75.15±13.03	1.66	0.112
MBP	90.52±14.84	93.57±16.16	1.34	0.195
SPAP	60.75±8.77	60.1±8.05	1.55	0.137
DPAP	34.05±5.75	32.4±8.16	1.2	0.23
mPAP	42.95±5.77	41.63±7.57	1.59	0.128
CVP	8.6±2.6	9.5±2.2	1.77	0.09
LVEF	43.1±7.37	45.65±5.71	1.6	0.118
FS	23.1±3.85	23.5±3.4	0.45	0.656
PaO_2/FiO_2 ratio	260.25±43.478	251.85±47.289	1.71	0.103

Data are expressed as mean±SD. CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FS, fractional shortening; HR, heart rate; LVEF, left ventricular ejection fraction; MBP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PaO_2/FiO_2, pressure of oxygen/fraction of inspired oxygen ratio; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; *t*, paired *t* test.

The routes of administration of milrinone were compared in a study by Wang *et al.* [13]; they included 48 patients who had PH after mitral valve surgery. The study population was divided into two groups, the first group of patients received milrinone by inhalation and the second group received the same drug through the intravenous route. In both groups, after milrinone administration, mPAP and pulmonary vascular resistance decreased. However, in the intravenous milrinone group, there was a significant decrease in the hemodynamic parameters, the MBP, and systemic vascular resistance compared with the inhaled group. In addition, in the inhaled group, there was an improvement in PaO_2/FiO_2 ratio in the inhaled milrinone group, which goes in parallel with our study.

A recent study by Theodoraki and colleagues compared inhaled milrinone versus inhaled iloprost in 48 patients subjected to elective cardiac operations with severe PH (SPAP >55 mmHg or mPAP >25 mmHg) as diagnosed by transthoracic echocardiography. The mPAP was significantly reduced at 10, 20, and 40 min after the beginning of inhalation as compared with baseline mPAP before inhalation with no significant change in MAP or CVP, which indicates no changes in systemic hemodynamics similar to our study; however, the average age in milrinone group was 74 years. In contrast, it was only 45 years in our study [4].

A study by Yutseven *et al.* [4] found that nitroglycerin inhalation resulted in a significant decrease in mPAP and pulmonary vascular resistance when used in a dose of 2.5 μg/kg/min nebulized by an air jet device for 5 h without affecting MAP, HR, or CVP. Moreover, PaO_2/FiO_2 ratio showed statistically significant improvement as in our study. However, the targeted patients studied by Yutseven and colleagues *et al.* were patients having mPAP over 25 mmHg.

In 1999, Omar and colleagues studied the effect of inhaled nitroglycerin in PH resulting from congenital cardiac diseases, and they found that SPAP and mPAP decreased after nitroglycerin inhalation; however, other hemodynamic parameters were not affected, which goes in parallel with our study [14].

Another study by Yurtseven and Karaca found the same results, when they compared the effects of inhaled nitroglycerin and iloprost in 100 patients with PH (mean PAP <25 mmHg) undergoing mitral valve replacement. With nitroglycerin administration at a dose of 20 μg/kg, they found that mPAP and pulmonary vascular resistance decreased significantly after treatment as compared with baseline. However, there were no significant differences concerning baseline hemodynamic parameters [15].

On the contrary, Bando and Kitamura, investigated the effects of inhalation of nitroglycerin at a dose of 2.5 μg/kg/min on hypoxic pulmonary vasoconstriction in dogs. They revealed that nitroglycerin inhalation decreased systemic pressures, pulmonary pressures, and pulmonary vascular resistance index but had no effect on cardiac output. This could be due to different hemodynamics in dogs [16].

Our results showed that inhalation of both milrinone and nitroglycerin proved to be safe and effective treatments for PH as they caused selective pulmonary vasodilatation avoiding systemic adverse effects, and they resulted in a decrease in mPAP, SPAP, and DPAP. These favorable effects of both drugs on the pulmonary blood vessels were confirmed by echocardiography and clinical measurements of the other hemodynamic parameters.

In addition, inhalation of both agents did not show systemic adverse effects, namely, reduction of systemic vascular resistance and hypotension. According to our results, there was no significance between the two groups, so inhaled

Table 8: Data of nitroglycerin group before and after delivery of the drug

	T1 (*n*=20)	T2 (*n*=20)	*t*	*P*
HR	102.25±32.78	96.45±9.16	0.914	0.37
SBP	128.9±29.72	133.2±22.73	0.48	0.63
DBP	67.9±10.39	73.45±14.31	1.49	0.15
MBP	89.48±14.4	91.87±18.85	0.46	0.65
SPAP	60.3±8.6	52.85±9.7	8.7	< 0.001
DPAP	34.05±5.67	27.53±6.61	4.75	< 0.001
mPAP	42.8±5.42	35.97±5.92	7.024	< 0.001
CVP	8.6±1.57	9.05±2.74	1	0.33
LVEF	44.1±10.26	42.3±7.28	1.125	0.27
FS	21.8±5.26	21.1±3.74	0.83	0.42
PaO_2/FiO_2 ratio	261.25±43.48	274.15±41.21	3.56	0.002

Data are expressed as mean±SD. CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FS, fractional shortening; HR, heart rate; LVEF, left ventricular ejection fraction; MBP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PaO_2/FiO_2, pressure of oxygen/fraction of inspired oxygen ratio; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; *t*, paired *t* test.

Table 9: Data of nitroglycerin group before delivery of the drug and before extubation

	T1 (*n*=20)	T3 (*n*=20)	*t*	*P*
HR	102.25±32.78	93.05±11.6	1.3	0.21
SBP	128.9±29.72	132.7±23.57	0.43	0.68
DBP	67.9±10.39	70.95±9.23	1.06	0.3
MBP	89.48±14.4	94.72±12.64	1.5	0.15
SPAP	60.3±8.6	60.2±9	0.346	0.733
DPAP	34.05±5.67	33.65±5.28	1.55	0.138
mPAP	42.8±5.42	42.5±5.39	1.77	0.092
CVP	8.6±1.57	9.5±1.73	1.99	0.061
LVEF	44.1±10.26	43.35±5.19	1.39	0.698
FS	21.8±5.26	21.95±2.37	0.136	0.89
PaO_2/FiO_2 ratio	261.25±43.48	259.8±47.02	0.15	0.88

Data are expressed as mean±SD. CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FS, fractional shortening; HR, heart rate; LVEF, left ventricular ejection fraction; MBP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PaO_2/FiO_2, pressure of oxygen/fraction of inspired oxygen ratio; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; *t*, Student *t* test.

nitroglycerin proved to be an effective, easy used, inexpensive, available, and safe alternative for the treatment of PH in mechanically ventilated patients after mitral valve replacement surgeries.

Our study has a few limitations, such as a limited number of patients were included, the dosage of nitroglycerin was similar to that doses used in the available literature, and the dose for milrinone used in our study was 50 µg/kg, which is based on Haraldsson *et al.* [11], Sablotzki and Starzmann [12], Singh and Choudhury [17], Denault and Haddad [18], Nguyen and Theoret [19] and is in accordance with previous studies [8].

The dose we used may be low for a stable hemodynamic effect. A stronger prominent effect may be obtained using a higher dose, and a comparison of different doses can be studied in future studies. Another limitation is that the mode of delivery of the inhaled drug makes it difficult to calculate the exact dose of the agent reaching the alveolar space [20].

Our study showed that both inhaled nitroglycerin and inhaled milrinone showed no adverse effects; it may be that the study was too small to determine other adverse effects associated with inhaled milrinone or inhaled nitroglycerin administration.

Conclusion

Both nitroglycerine and milrinone when inhaled are effective pulmonary vasodilators. The great benefit achieved from the inhalation route of administration is pulmonary selectivity, which caused a marked reduction in pulmonary artery pressure in addition to avoiding the systemic adverse effects, namely, the decrease in peripheral vascular resistance and hypotension. According to the results of our study, which included a limited number of patients, the administration of a specific dose of inhaled nitroglycerin or inhaled milrinone resulted in selective pulmonary vasodilatation in patients with PH following mitral valve surgery. According to our results, inhaled nitroglycerin appears to be an effective, easy-to-administer, inexpensive, available, and safe alternative for the treatment of PH in mechanically ventilated patients after mitral valve replacement surgeries.

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Conflicts of interest

There are no conflicts of interest.

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