Original research

Early and mid-term outcome of inhaled versus intravenous milrinone in patients with rheumatic mitral stenosis and pulmonary hypertension undergoing mitral valve surgery

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Abstract

Objective: Inhalational milrinone (iMiL) leads to reduction in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) in patients suffering from pulmonary arterial hypertension (PAH) with use of systemic vasodilatation compared to intravenous milrinone (IVMil).

Our study was aimed to compare the effect of inhaled versus intravenous milrinone on perioperative and mid-term outcome in patients with rheumatic severe mitral stenosis (MS) with severe PAH undergoing mitral valve replacement surgery.

Methods: Between September 2017 to December 2019, a prospective observational study was performed in 150 patients with severe MS and right ventricular (RV) systolic pressure >50 mm Hg. They were divided into two groups i.e., iMil and IVMil. Various outcomes along with hemodynamic and echocardiographic parameters at baseline and at 4 different time points were noted.

Results: Mean age was 35.7 (8.2) years. There were 5 deaths (1 in iMil group and 4 in IVMil group p= 0.023) and all deaths were due to acute RV failure. In iMil group, there was significant improvement in RV fractional area change (T1 to T3, p<0.001) and TAPSE parameters (T1 p<0.001, T2 p=0.004, T3 p=0.02), significant reduction in PAP and PVR (T1 to T3, p<0.001, respectively); while lesser fall in systemic vascular resistance (T1 to T3, p<0.001) compared to IVMil group. Vasopressor-inotropic score was significantly higher in IVMil group (at shifting p<0.001, after 24 hrs p<0.001, after 48 hrs p=0.002, after 72 hrs p=0.002). During follow-up, patients in both the groups had excellent survival with good functional outcomes.

Conclusion: Intraoperative inhalational milrinone improves RV and systemic hemodynamics better than intravenous milrinone. It is also superior to intravenous milrinone to prevent acute RV failure, which ultimately leads to significant reduction in post-operative morbidity and mortality.

Key words: rheumatic mitral stenosis, pulmonary arterial hypertension, nebulization cardiopulmonary bypass, milrinone

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Introduction

The management of those patients with pulmonary artery hypertension (PAH) and rheumatic disease causing citral stenosis undergoing mitral valve surgery poses a difficult clinical challenge. PAH associated with rheumatic mitral stenosis (MS) increases the risk of perioperative morbidity and mortality in patients undergoing mitral valve replacement (MVR) (1, 2). Several perioperative factors including cardiopulmonary bypass (CPB), blood transfusion, protamine, hypoxia, hypercarbia, positive pressure ventilation, and left ventricular (LV) dysfunction are to to acutely worsen the pre-existing PaH and increase right ventricular (RV) afterload (3, 4). RV output is afterload sensitive, and sudden elevation of afterload leads to rapid dilatation and contractile dysfunction of RV, reduced LV preload and systemic arterial pressure, and reduced coronary perfusion pressure (5-9). All these together lead to delay in weaning from CPB, prolonged mechanical ventilation, and increased morbidity and mortality (10).

Among the available therapeutic strategies, the choice between the use of inhaled drugs and intravenous drugs poses a critical decision, which significantly impacts clinical outcomes (11-18).

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Graphical abstract

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Outcomes of patients with MVD underwent MVR with inhalational and intravenous milrinone				
Variables		iMil Group	IVMil Group	p
RV Dysfunction, n(%)		8 (10.66)	24 (32)	<0.0001
Acute RV failure, n(%)		1 (1.33)	5 (6.66)	0.009
Difficult weaning off CPB, n(%)		1 (1.33)	8 (10.66)	0.008
Vasoplegia syndrome, n(%))		4 (5.33)	18 (24)	<0.0001
VIS Score	At Shifting	13.8 (3.3)	18.3 (5.1)	<0.0001
	After 24 hours	11.9 (3.1)	17.6 (5.2)	<0.0001
	After 48 hours	8.8 (2.8)	14.3 (5.4)	<0.0001
	After 72 hours	3.7(1.3)	6.3 (7.1)	0.002
Mechanical ventilation >48 hours, n(%)		4 (5.33)	13 (17.33)	0.020
Death, n(%)		1 (1.33)	4 (5.33	0.023

In iMil group, there was significant improvement in RV FAC (T1 to T3, p<0.001) and TAPSE (T1 p<0.001, T2 p=0.004, T3 p=0.02), significant reduction in PAP and PAR (T1 to T3, p<0.001, respectively); while lesser fall in SVR (T1 to T3, p<0.001) compared to IVMil group.

Milrinone, which can be used in both ways as inhalation or intravenous injection, is a phosphodiesterase III inhibitor and in acts by positive inotropic action and vasodilation, has shown to be a valuable therapeutic option in the management of perioperative care of such patients (19-21).

This study aims to investigate and compare the clinical outcomes associated with the use of inhaled milrinone versus intravenous milrinone in patients suffering from rheumatic MS and PAH undergoing mitral valve surgery. The study seeks to identify the efficacy, safety, and overall impact of these two available therapeutic modes of milrinone administration on perioperative parameters and postoperative recovery.

By direct inhalation of milrinone, there is a potential to deliver the milrinone directly to pulmonary vasculature, which targets the primary site of pathology in these patients. In contrast, the intravenous administration of milrinone may result in systemic effects, especially both cardiac and peripheral vascular effects. By comparing these two modes of administration of milrinone, we aim to elucidate any superiority in optimizing hemodynamic stability, reducing pulmonary vascular resistance, and enhancing postoperative recovery between the two groups.

By comparing the clinical data, including perioperative hemodynamics, duration of mechanical ventilation, incidence of postoperative complications, and overall mortality rates, this study seeks to contribute evidence-based recommendations for the optimal use of milrinone in patients with rheumatic MS and PAH undergoing mitral valve surgery. These findings help to guide clinicians in making informed decisions, and hence improving the quality of care and outcomes for the specific patient population.

In our institute, based on surgeon preference, we have been using either intra-operative iMil at two time points or milrinone loading after the release of cross clamp in patients undergoing MVR with PAP >50mmHg. In a previous study from our institute, we reported that iMil leads to significant decrease in PAP, pulmonary vascular resistance index (PVRI) without significant change in systemic arterial pressure and systemic vascular resistance index (SVRI) (12).

Embolden by our own previous results, we desiged this prospective observational study to compare the hemodynamic effects of iMil and IVMil in postoperative period and their effect on various parameters and clinical outcome in terms of morbidity and mortality in the postoperative period and during follow-up in patients with rheumatic severe MS with severe PAH undergoing MVR at our institute.

Methods

Study design and population

This was prospective observational study in nature. Between September 1, 2017, to December 31, 2019, total 150 patients with rheumatic heart disease with severe MS with or without concomitant mitral regurgitation and with or without severe tricuspid regurgitation (TR) with severe PAH (PAP > 50mmHg) on transthoracic echocardiography (TTE) and planned for MVR with or without tricuspid valve (TV) repair were included.

Exclusion criteria were emergency surgery, preoperative inotropic support, bronchial asthma, pulmonary thromboembolic disease, renal or hepatic dysfunction, bleeding diatheses, or thrombocytopenia. Criterion for the preoperative PHT was an estimated RV systolic pressure using the peak velocity of tricuspid valve regurgitation jet in TTE.

All the patients were divided in two groups: iMil group - 75 patients and ivMil group - 75 patients.

Study was approved by the Ethics committee of our institute (UNMICRC/C.ANESTHESIA/2017/02), and written informed consent was obtained from all participants.

Baseline variables

The following variables were assessed: age, sex, severity of MS, NYHA class, body mass index (BMI), type of surgery and medical treatment.

Study protocol, anesthesia management and surgical procedure

All the patients included in the study were induced as per the institutional anesthesia protocols that include administration of midazolam 0.1 mg/kg, fentanyl 5 mg/kg and vecuronium 0.15 mg/kg. All the patients were put on volume-controlled ventilation post intubation. Ventilatory settings kept as per institutional protocol i.e. Tidal volume of 8 mL/kg, respiratory rate of 12–14 breaths/min with air and oxygen with fraction of inspired oxygen (FiO2) 0.5. During the surgery, anesthesia was maintained with sevoflurane (1.5 MAC) and intermittent injection of fentanyl, midazolam and vecuronium. Intra-operative monitoring included central venous pressure monitoring through a Swan-Ganz catheter, electrocardiogram, pulse oximetry, a femoral artery catheter for invasive blood pressure monitoring and capnography.

An adult trans-esophageal echocardiography (TEE) probe was inserted in all patients and kept throughout the surgical procedure for intra-operative monitoring. Surgical approach was through midline sternotomy with moderate hypothermic cardio-pulmonary bypass (CPB). For CPB, the ascending aorta and both the vena-cava were cannulated, and cardiac arrest was achieved and maintained using intermittent doses of modified St. Thomas blood cardioplegia. During CPB, pump flow was adjusted to 2.2 L/min per m^2, and mean arterial pressure (MAP) was maintained at 60–75 mm of Hg by adjusting the pump flow and administering phenylephrine as and when required.

Mitral valve replacement with total chordal preservation was carried out through Waterston's groove or by a transseptal approach in patients who required concomitant tricuspid valve repair. After completion of the procedure, the heart was deaired, the aortic cross-clamp (ACC) was released, and the aortic root was vented. When the heart regained rhythm with good contractility and systemic temperature was > 36°C, the patient was weaned off CPB. After all the cannula were removed, heparin was reversed by injection protamine in a ratio of 1: 1 (12).

Milrinone

All the patients were divided in two groups based upon the strategy they received to reduce the PAH. In inhalational iMil group - 75 patients received inhaled milrinone immediately after sternotomy and after removal of aortic cross-clamp, while in IVMil group - 75 patients received intravenous loading dose of milrinone (50µg/kg body weight) at release of aortic cross-clamp. Both the treatments were as per standard protocol of our institute.

Hemodynamic variables

All patients were monitored with pulmonary artery catheter, electrocardiogram, pulse oximetry, capnography, and radial artery catheter.

Various hemodynamic data: Central venous pressure (CVP), cardiac index (CI), fraction of inspired oxygen (FiO2), mean arterial pressure (MAP), mixed venous oxygen saturation (MVO_2), mean pulmonary artery pressure (MPAP), partial pressure of oxygen (PaO2), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance index (PVRI), pulmonary shunt fraction (Qs/Qt), systolic pulmonary artery pressure (SPAP), SVRI-systemic vascular resistance index (SVRI), transpulmonary gradient (TPG) and vasoactive-inotropic score (VIS) (22) were collected. VIS was recorded at different time frames: T0- baseline before sternotomy; T1- before shifting to intensive care unit (ICU); T2- 12 hours after shifting to ICU; T3- 24 hours after shifting to ICU; T4- 48 hours after shifting to ICU. VIS score was calculated using this formula:

VIS = dopamine dose [μg/kg/min] + dobutamine dose [μg/kg/min] + 100 × epinephrine dose [μg/kg/min] + 10 × milrinone dose [μg/kg/min] + 10,000 × vasopressin dose [U/kg/min] + 100 × norepinephrine dose [μg/kg/min]) (22).

Echocardiography

Tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RVFAC), RV end- systolic area (RVESA) and RV end-diastolic area (RVEDA), left ventricular ejection fraction (LVEF), right ventricular myocardial performance index (RVMPI) and SPAP were measured using TEE during surgery and TTE before and after surgery with a Hewlett-Packard Sonos 5500 machine (Hewlett-Packard, Inc., Andover, MA, USA) by experienced operator using standard guidelines (23). In addition, left ventricle and mitral valve were assessed for function, gradient, and paravalvular leak. The tricuspid valve was also assessed for regurgitation and stenosis (23).

After completion of the procedure, patients were shifted to intensive care unit (ICU) intubated and managed as per ICU protocol. After shifting to ICU, various echocardiographic parameters mentioned above were noted with TEE in intubated patients and with TTE in extubated patients using same machine.

Follow-up

Patients were also followed-up after discharge at 1 month, 3 months, 6 months and then 6 monthly. In each visit, their clinical outcome and echocardiography data were noted.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (SPSS, Inc., Chicago, IL, USA). Data are expressed as mean (standard deviation) or number and percentage, as appropriate. The Independent Student`s t test for continuous variables and the Chi-square test for categorical variables were used for comparisons of measurements and calculations between the two groups at each time point. A value of $p<0.05$ was considered statistically significant.

RESULTS

Mean age of the patients was 35.7(8.2) years (range 21-58 years). All patients underwent MVR with (86 patients) or without (64 patients) TV repair. Mean PAP was 63.8 (17.3) mmHg (range 53mmHg - 106mmHg). Twenty-seven patients in both the groups had an evidence of RV dysfunction (TAPSE <16mm, RVFAC <35%). All the demographic and clinical variables age, sex, weight, BMI, NYHA Class, echocardiographic parameters and drug therapy aree presented in Table 1 .

Hemodynamic parameters (Table 2)

Effects of iMil and IVMil on systemic and pulmonary hemodynamics at different time points are shown in Table 2. Baseline systemic and pulmonary hemodynamic parameters were comparable in both the groups.

There was no significant change in systemic arterial pressure and mixed venous oxygen saturation in either group at different time points. After surgery CVP, PCWP, PAP, TPG, SVRI, and PVRI decreased in both groups. All these parameters remained significantly lower in iMil group compared to IVMil group ($p<0.0001$) for initial 24 hours. The difference, however, became non-significant subsequently. Despite the reduction in PCWP, TPG increased in IVMil group while it remained unchanged in iMil group early after surgery. Cardiac index increased in both the groups, however, increase in CI was significantly more in iMil group at all-time points ($p<0.05$). For SVRI and PVRI, decrease in SVRI was significantly less while decrease in PVRI was significantly more in iMil group as suggested by PVRI/SVRI ratio for initial 24 hours after surgery ($p<0.0001$). PaO2/FiO2 ratio improved in both the groups early after surgery (iMil group > IVMil group) and remained improved, subsequently. The same is confirmed by decrease in the intrapulmonary blood shunting fraction (Qs/Qt ratio).

Table 1. Demographic, clinical, preoperative and postoperative data of patients

Variables	Group iMil (n=75)	Group IV Mil (n=75)	p
Age, years	34.97 (7.76)	36.28 (8.83)	0.336
Sex, M/F, n	(42/33)	(45/30)	0.620
Weight, kg	48.8 (5.7)	47.5 (4.8)	0.133
BMI, kg/m^2	19.7±1.7	20.1±1.8	0.163
NYHA class, n(%) 1	7 (10)	6 (8)	1.000
2	20 (26)	21 (28)	1.000
3	41 (54)	39 (52)	1.000
4	7 (10)	9 (12)	1.000
Transthoracic echocardiography			
MS, n(%)	51 (68)	47.0(62.66)	0.492
MS with MR, n(%)	24 (32)	28.0(37.33)	0.606
TR , n(%) Mild	8.0(10.66)	8.0(10.66)	0.791
Moderate	31.0 (41.33)	38.0 (50.66)	0.481
Severe	36 (48)	29.0 (38.66)	0.717
SPAP, mmHg	67.8 (13.1)	68.1 (17.0)	0.901
TAPSE, mm	17.0 (2.3)	18.0 (2.4)	0.155
RVFAC, %	38.5 (3.1)	39.2 (2.9)	0.758
RV Dysfunction, n(%)	17 (22.66)	10 (13.33)	0.137
LVEF, %	55.0 (4.1)	55.6 (3.3)	0.325
Type of surgery, n(%)			
MVR	28 (46)	36 (52)	0.187
MVR + TV Repair	47 (54)	39 (48)	0.247
Drug therapy at admission, n(%)			
Beta-blockers	75 (100)	75 (100)	1.000
ACE inhibitors	13 (18)	7 (9.3)	**0.04**
Digoxin	26 (39)	40 (56)	**0.021**
Diuretics	75 (100)	75 (100)	1.000
Duration of surgery, min	226.0(35.6)	235.0 (31.6)	0.104
CPB duration, min	67.4 (17.3)	63.5 (15.5)	0.148
ACC duration, min	49.6 (15.7)	48.4 (14.5)	0.627

Data are presented as mean (SD) and as n(%)
ACC- aorta cross-clamp time, ACE- angiotensin converting enzyme, BMI- body mass index, CPB- cardiopulmonary bypass time, LVEF- left ventricular ejection fraction, MR- mitral regurgitation, MS- mitral stenosis, MVR- mitral valve replacement, NYHA- New York Heart Association, RV- right ventricle, RVFAC - RV fractional area change, SPAP- systolic pulmonary artery pressure, TR-tricuspid regurgitation, TV - tricuspid valve, VIS- vasoactive inotropic score

Table 2. Change in hemodynamic and intraoperative parameters at different time points in both the groups

Variables	Group	Baseline T0	At shifting T1	Time Point T2	Time Point T3	Time Point T4
MAP, mmHg	**iMil**	72.6 (4.1)	71.3 (4.6)	76.4 (5.2)	79.3 (4.8)	73.2 (4.1)
	IVMil	73.4 (3.2)	70.8 (3.4)	74.7 (5.8)	77.9 (4.1)	71.9 (4.2)
p		0.185	0.450	0.06	0.06	0.06
CVP, mmHg	**iMil**	9.1 (2.9)	5.5 (4.5)	6.2 (3.8)	5.4 (4.2)	6.0 (5.1)
	IVMil	9.9 (2.6)	8.4 (3.1)	8.36 (5.3)	7.4 (4.3)	6.2 (2.3)
p		0.077	**<0.0001**	**<0.0001**	**0.004**	0.757
PCWP, mmHg	**iMil**	29.2 (4.3)	12.3 (3.6)	13.5 (2.9)	13.9 (3.5)	13.32 (2.4)
	IVMil	29.12 (3.7)	18.8 (2.9)	16.3 (3.8	18.3 (2.7)	14.3 (4.1)
p		**0.90**	**<0.0001**	**<0.0001**	**<0.0001**	0.07
SPAP, mmHg	**iMil**	70.5 (11.1)	41.6 (9.6)	40.32 (7.5)	41.9 (6.2)	42.3 (6.3_
	IVMil	67.6 (10.4)	56.7 (11.1)	53.7 (8.2)	52.6 (7.7)	44.2 (6.54)
p		0.101	**<0.0001**	**<0.0001**	**<0.0001**	0.07
MPAP, mmHg	**iMil**	48.7 (9.43)	30.2 (6.8)	26.5 (5.9)	27.23 (4.7)	29.32(5.3
	IVMil	47.8 (10.2)	43.6 (8.2)	40.42 (6.5)	35.43 (6.2)	31.11(7.4
p		0.579	**<0.0001**	**<0.0001**	**<0.0001**	0.09
TPG, mmHg	**iMil**	19.5 (4.2)	17.9 (4.6)	13 (3.9)	13.33 (5.4)	16.0 (4.7)
	IVMil	18.7 (5.4)	24.8 (4.8)	24.12 (4.1)	17.13 (6.3)	16.81 (5.6)
p		0.31	**<0.0001**	**<0.0001**	**0.0001**	0.33
CI, L/min	**iMil**	2.39 (0.45)	3.63 (0.46)	3.89 (0.39	3.35 (0.41)	3.32 (0.36)
	IVMil	2.41 (0.48)	2.85 (0.49)	2.93 (0.38	2.85 (0.53)	3.12 (0.39)
P		0.793	**<0.0001**	**<0.0001**	**<0.0001**	**0.001**
SVRI, dynes-sec/cm^{-5}/m^2	**iMil**	2621.9 (290.0)	2134.2(320.0)	2144 (222)	2252.2 (180.0)	2490.2 (215.0)
	IVMil	2594.2 (301.0)	1885.7(314.0)	1850.5(264.0)	2003.4(243.0)	2435.5(211.0)
p		0.567	**<0.0001**	**<0.0001**	**<0.0001**	0.118
PVRI, dynes-sec/cm^{-5}/m^2	**iMil**	676.7 (106.0)	354.4 (117.0)	440.4 (72.0)	429.9 (66.0)	487.7 (58.0)
	IVMil	659.9 (104.0)	608 (96.0)	583.6 (78.0)	514.4 (75.6)	500.3 (66.0)
p		0.329	**<0.0001**	**<0.0001**	**<0.0001**	0.19

Data are presented as Mean (SD)

Table 2. Change in hemodynamic and intraoperative parameters at different time points in both the groups (continued from page ???)

Variables	Group	Baseline T0	At shifting T1	Time Point T2	Time Point T3	Time Point T4
PVRI/SVRI	**iMil**	0.26 (0.05)	0.16 (0.03)	0.20 (0.05)	0.19 (0.04)	0.195 (0.03)
	IVMil	0.25 (0.01)	0.32 (0.04)	0.31 (0.04)	0.25 (0.04)	0.20 (0.045)
p		0.091	**<0.0001**	**<0.0001**	**<0.0001**	0.33
PaO2/FiO2	**iMil**	241.8 (62.1)	344.8 (68.4)	372.3 (62.6)	391.2 (61.8)	395.6 (57.5)
	IVMil	225.0 (64.6)	336.1 (60.4)	355.2 (69.3)	405.3 (56.5)	386.5 (45.9)
p		0.107	0.410	0.11	0.147	0.286
MvO2 (%)	**iMil**	62.6 (6.6)	66.1 (5.1)	62.6 (3.7)	64.5 (3.9)	60.6 (4.6)
	IVMil	64.3 (4.9)	64.6 (4.6)	63.7 (4.2)	63.2 (4.9)	59.44 (4.5)
p		0.075	0.06	0.09	0.074	0.137
Qs/Qt	**iMil**	31.1 (3.9)	19.6 (3.8)	19.4 (4.3)	18.5 (3.8)	21.6 (3.7)
	IVMil	29.8 (5.1)	19.8 (3.2)	18.8 (4.9)	19.7 (3.1)	23.1 (4.1)
p		0.08	0.728	0.427	**0.036**	**0.020**

Data are presented as mean (SD)
CI- cardiac index, CVP-central venous pressure, FiO2-fraction of inspired oxygen, MAP- mean arterial pressure, MPAP-mean pulmonary artery pressure, MVO2- mixed venous oxygen saturation, PaO_2- partial pressure of oxygen, PCWP-pulmonary capillary wedge pressure, PVRI- pulmonary vascular resistance index, Qs/Qt- pulmonary shunt fraction, SPAP-systolic pulmonary artery pressure, SVRI-systemic vascular resistance index, TPG- transpulmonary gradient

Echocardiographic parameters (Table 3)

TEE demonstrated that there was no significant change in LVEF in both the groups. Both, TAPSE and RVFAC improved in iMil group ($p<0.05$) while it reduced in IVMil group immediately after surgery and then improved subsequently ($p<0.05$ for both). For initial 24 hours after surgery, both TAPSE and RVFAC were significantly higher in iMil group ($p<0.05$). RVMPI reduced after surgery and remained significantly lower in iMil group at all-time points ($p<0.05$). Right ventricular volumes as measured by RVEDV and RVSEV reduced in both the groups ($p<0.05$). Reduction in RVESV was comparable in both the groups while reduction in RVEDV in iMil group was significantly more ($p<0.05$).

Postoperative VIS score, morbidity and mortality (Table 4)

Total 32 patients (8 in iMil group and 24 in IVMil group) developed RV dysfunction after surgery. Out of these 32 patients, 23 patients (7 in iMil group and 16 in IVMil group) were weaned off CPB without difficulty while 9 patients (1 in iMil group and 8 in IVMil group) had difficulty in weaning off CPB. Three patients in IVMil group had mild RV dysfunction and were weaned successfully after supportive bypass without escalation of vasopressors. Remaining 6 patients in (1 in iMil group and 5 in IVMil group) developed acute RV failure and required escalation of vasopressor to maintain MAP >65mmHg and separation from CPB. Total 22 patients developed vasoplegia syndrome (4 in iMil group, 18 in IVMil group) including 6 patients who developed acute right failure. VIS score was significantly higher in IVMil group compared to iMil group (18.3 (5.1) v/s 13.8 (3.3), respectively) ($p<0.001$) and remained higher till time point T4. There were no statistical differences in the amount of blood loss, blood transfusion, ventilation time, ICU stay and mean hospital stay between two groups. There were 5 deaths (4 in IVMil group and 1 in iMil group).

Table 3. Change in echocardiographic parameters at different time points in both the groups

Variables	Group	Baseline T0	At shifting T1	Time Point T2	Time Point T3	Time Point T4
TAPSE, mm	**iMil**	14.6 (3.1)	15.8 (1.9)	16.0 (2.1)	16.5 (1.7)	17.4 (1.9)
	IVMil	14.7 (3.0)	13.4 (2.7)	14.7 (2.3)	15.4 (2.5)	16.9 (1.7)
p		0.841	**<0.0001**	**0.0004**	**0.002**	**0.09**
RVFAC, %	**iMil**	35.5 (3.4)	38.7 (3.4)	39.5 (3.3)	40.7 (2.9)	40.3 (3.0)
	IVMil	36.3 (3.3)	34.9 (3.0)	36.1 (3.1)	38.5 (3.5)	39.3 (3.9)
p		0.146	**<0.0001**	**<0.0001**	**<0.0001**	**0.08**
RVMPI	**iMil**	0.33 (0.03)	0.30 (0.03)	0.30 (0.04)	0.29 (0.02)	0.27 (0.02)
	IVMil	0.31 (0.03)	0.34 (0.03)	0.33 (0.03)	0.31 (0.03)	0.29 (0.02)
p		**0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
RVESA, cm^2	**iMil**	23.7 (3.0)	20.3 (2.9)	20.5 (2.4)	19.2 (2.3)	19.2 (2.0)
	IVMil	23.0 (3.5)	21.7 (3.4)	21.4 (3.1)	20.5 (3.3)	19.9 (3.0)
p		**<0.0001**	**0.007**	**0.0009**	**0.006**	0.095
RVEDA, cm^2	**iMil**	36.4(5.9)	33.3 (4.8)	32.0 (4.4)	32.0 (4.0)	30.8 (4.1)
	IVMil	35.8(5.1)	33.9 (4.7)	33.1 (5.1)	32.0 (4.9)	31.4 (5.1)
p		0.508	0.440	0.159	1.000	0.428
LVEF, %	**iMil**	56.8 (3.3)	56.0 (3.6)	55.9 (3.1)	56.4 (3.3)	56.5 (3.0)
	IVMil	55.9 (3.5)	56.1 (3.9)	55.6 (4.1)	56.0 (3.0)	56.1 (3.1)
p		0.107	0.856	0.614	0.439	0.423

Data are presented as mean (SD)
LVEF-left ventricular ejection fraction, RVEDA-right ventricular end-diastolic area, RVMPI-right ventricular myocardial performance index, RVFAC - RV fractional area change, RVESA-right ventricular end- systolic area, TAPSE-tricuspid annular plane systolic excursion

Comparison of hemodynamic and TEE parameters in death and survivors (Table 5, 6)

Analysis of TEE data showed that all expired patients developed acute right heart failure as suggested by marked decrease in TAPSE and RVFAC and marked increase in RVMPI with normal LV function ($p<0.05$). In hemodynamic parameters, patients who expired had significantly lower MAP and CI ($p<0.05$ for both). They also had SVRI value of <1800 dynes-sec/cm5/m2 after weaning from CPB and remained lower despite escalation of vasopressors. Further, CVP, TPG, systolic PAP and PVRI also remained significantly higher in expired patients ($p<0.05$ for all). All these parameters deteriorated over initial 48 hours after surgery.

Table 4. Comparison of postoperative morbidity and mortality data in both the groups			
Variables	**Group iMil (n=75)**	**Group IV Mil (n=75)**	**p**
RV dysfunction, n(%)	8 (10.66)	24 (32)	**<0.0001**
Acute RVF, n(%)	1 (1.33)	5 (6.66)	**0.009**
Difficult weaning off CPB, n(%)	1 (1.33)	8 (10.66)	**0.008**
Vasoplegia syndrome, n(%)	4 (5.33)	18 (24)	**<0.0001**
VIS Score, n(%) At Shifting	13.8(3.3)	18.3(5.1)	**<0.0001**
After 24 Hours	11.9(3.1)	17.6(5.2)	**<0.0001**
After 48 Hours	8.8(2.8)	14.3(5.4)	**<0.0001**
After 72 Hours	3.7(1.3)	6.3(7.1)	**0.002**
Mediastinal bleeding, ml (Range)	480(105) (190–750)	460(125) (200–750)	0.294
Blood transfusion, ml (Range)	500(110) (250–750)	460(140) (250–750)	0.053
Re-exploration, n(%)	1 (1.33%)	2 (2.66%)	0.154
Mechanical ventilation, hours (Range)	11.4 (5.4) (4-33)	12.4(16.4) (3-99)	0.617
Mechanical ventilation >48 Hours, n(%)	4 (5.33)	13 (17.33)	**0.020**
ICU stay, hours, (Range)	38.32 (8.14) (26-96)	39.91(15.94) (24-266)	0.443
Hospital stay, days (Range)	5.18(1.04) (4-10)	4.98(1.97) (4-21)	0.438
Death, n(%)	1.0 (1.33)	4 (5.33)	**0.023**

Continuous variables are presented as mean (SD) and categorical as n(%)
CPB- cardiopulmonary bypass, ICU- intensive care unit, VIS- vasopressor inotropic score

Follow-up (Table 7)

Follow-up was 100% complete in both groups and mean duration of follow-up was 33.5 (4.2) months in iMil group, while 32.7(4.4) months in IVMil group. During follow-up, almost 95% patients were in NYHA class I or II in both the groups. There were total 6 deaths in both the groups (3 in iMil group, 3 in IVMil group). There was no difference between the groups in terms of complications and deaths during follow-up (24).

Discussion

In patients with severe PAH due to MS, aggravation of pulmonary artery pressure early after weaning from CPB is an important predictor of outcome (1-3). Recently, compared to other available inhalators, inhaled milrinone vasodilator therapy gained popularity due to various reasons e.g. cheap price, avoidance of methemoglobinemia and ease of administration (25, 26). Milrinone has a rapid onset of action and has been proven in many studies to be effective in decreasing PAP after surgery (11-20). We have seen that despite having shorter duration of action milrinone prevents acute rising PAP post CPB and similar findings have been shown by others (19, 20). Our findings indicate that the effect is sufficient to prevent an acute post-CPB rise in PAP.

Table 5. Change in echocardiographic parameters at different time points in patients who survived and died

Variables	Group	Baseline T0	At shifting T1	Time Point T2	Time Point T3	Time Point T4
TAPSE, mm	**Survived**	14.6 (3.6)	14.7 (3.4)	15.8 (3.7)	16.0 (2.9)	16.5 (3.1)
	Died	14.7 (2.8)	10.4 (2.7)	8.6 (1.8)	8.4 (1.5)	9.1 (1.7)
p		0.85	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
RVFAC, %	**Survived**	35.6 (3.7)	37.8 (3.6)	38.3 (3.4)	39.8 (3.2)	39.8 (3.2)
	Died	36.5 (2.8)	31.8 (2.9)	26.4 (2.3)	20.9 (1.8)	24.6 (1.3)
p		0.095	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
RVMPI	**Survived**	0.33(0.03)	0.32(0.03)	0.31(0.04)	0.30(0.02)	0.28(0.02)
	Died	0.31(0.03)	0.34(0.02)	0.36(0.02)	0.38(0.02)	0.40(0.02)
p		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
RVESA, cm^2	**Survived**	23.7(3.0)	20.3(2.9)	20.5(2.4)	19.2(2.3)	19.2(2.0)
	Died	23.2(2.3)	21.8(2.4)	23.6(2.1)	25.5(1.9)	27.9(2.0)
p		0.254	**0.0007**	**<0.0001**	**<0.0001**	**<0.0001**
RVEDA, cm^2	**Survived**	36.1(5.7)	33.1(4.7)	32.0(4.3)	32.0(4.0)	30.5(3.7)
	Died	35.8(3.5	33.9(3.7	35.4(3.1	37.8(2.9	38.4(2.1
P		0.694	0.249	**<0.0001**	**<0.0001**	**<0.0001**
LVEF, %	**Survived**	56.6(3.3)	56.0(3.7)	55.7(3.4)	56.4(3.0)	56.2(3.0)
	Died	56.1(2.7)	56.0(2.9)	55.0(3.1)	56.0(2.0)	45.2(2.1)
P		0.311	1.000	0.19	0.338	**<0.0001**

Data are presented as mean (SD)
LVEF- left ventricular ejection fraction, RVEDA-right ventricular end- diastolic area, RVFAC – right ventricular fractional area change, RVMPI- right ventricular myocardial performance index, RVESA- right ventricular end-systolic area, TAPSE - tricuspid annular plane systolic excursion

Prevention of rise in PAP early after weaning from CPB is the most crucial factor in prevention of acute right heart failure (1-3). Our results show that the use of inhalational milrinone resulted in significantly greater reduction in CVP, PCWP, TPG, PVRI and PAP early after surgery and the effect remained sustained for 24 hours. We believe that these effects are mediated by superior direct pulmonary vasodilatory effect of inhalational milrinone on pulmonary vasculature. Reduction in PVRI results in decreased PAP, decreased RV afterload and improved RV function leads to improvement in CI. Higher cardiac index translates into improved end-organ perfusion which is critical for organs recovering from chronic low cardiac output state due to pre-existing severe MS and deleterious effects of CPB (11, 17).

Table 6. Change in hemodynamic parameters at different time points in patients who survived and died

Variables	Groups	Baseline T0	At shifting T1	Time Point T2	Time Point T3	Time Point T4
MAP, mmHg	**Survived**	71.4 (5.1)	72.3 (6.8)	78.7 (6.47)	77.2 (5.1)	78.1 (4.9)
	Died	71.6 (8.1)	69.8 (5.4)	56.7 (7.2)	55.6 (8.6)	50.2 (7.5)
p		0.933	0.418	**<0.0001**	**<0.0001**	**<0.0001**
CVP, mmHg	**Survived**	9.4 (4.9)	7.5 (3.2)	6.3 (2.7)	5.8 (2.9)	6.0 (2.7)
	Died	9.8 (4.6)	9.1 (2.4)	9.8 (4.3	9.4 (3.4)	9.9 (4.1)
p		0.858	**0.0007**	**<0.0001**	**0.007**	**0.002**
PCWP, mmHg	**Survived**	30.2 (6.7)	14.3 (5.4)	13.3 (3.0)	13.1 (2.4)	13.1 (2.1)
	Died	31.4 (7.3)	13.8 (4.9)	13.3 (3.4)	12.9 (2.9)	13.5 (3.61)
p		0.695	0.839	1.000	0.856	0.684
SPAP, mmHg	**Survived**	69.5 (17.2)	49.6 (10.7)	40.5 (6.9)	40.4 (8.1)	42.5 (7.9)
	Died	65.6 (16.4)	55.4 (14.5)	52.4 (12.6)	37.8 (8.8)	35.3 (8.6)
p		0.618	0.240	**0.0003**	**<0.0001**	**0.047**
MPAP, mmHg	**Survived**	47.7 (11.3)	33.2 (7.3)	27.3 (6.7)	25.9 (8.1)	24.8 (7.6)
	Died	46.8 (10.8)	38.6 (9.1)	28.9 (8.6)	24.2 (8.7)	22.2 (8.6)
p		0.861	0.109	0.603	0.646	0.456
TPG, mmHg	**Survived**	17.4 (6.1)	15.9 (4.3)	14.5 (4.0)	12.1 (4.3)	11.7 (4.1)
	Died	15.9 (6.8)	25.3 (6.3)	15.1 (5.6)	12.3 (5.3)	10.9 (5.2)
p		0.591	**<0.0001**	0.745	0.919	0.671
CI, L/min	**Survived**	2.44 (0.5)	3.44 (0.4)	3.44 (0.4)	3.42 (0.3)	3.4 (0.3)
	Died	2.54 (0.4)	3.41 (0.5)	2.48 (0.7)	2.16 (0.5)	2.06 (0.4)
p		0.659	0.870	**<0.0001**	**<0.0001**	**<0.0001**
SVRI, dynes-sec/cm^{-5}/m^2	**Survived**	2614.9 (313.23)	2410.5 (347.6)	2605.4 (231.0)	2620.2 (198.9)	2620.2 (232.5)
	Died	2524.2 (349.7)	1668.7 (301.0)	1548.5 (298.5)	1578.4(301.3)	1384.5(294.1)
p		0.527	0.127	**0.888**	**<0.0001**	**<0.0001**
PVRI, dynes-sec/cm^{-5}/m^2	**Survived**	646.7 (118.3)	517.3 (103.5)	475.4 (66.7)	451.3 (69.4)	468.7 (71.4)
	Died	657.9 (111.9)	610.3 (95.4)	575.6 (79.2)	540.4 (75.6)	500.3 (60.7)
p		0.835	**0.049**	**0.001**	**0.005**	0.330

Table 6. Change in hemodynamic parameters at different time points in patients who survived and died continued from page ??

Variables	Groups	Baseline T0	At shifting T1	Time Point T2	Time Point T3	Time Point T4
PVRI/SVRI	**Survived**	0.25 (0.05)	0.19 (0.04)*	0.22 (0.04)#@	0.19 (0.04)*	0.22 (0.04)#@
	Died	0.26 (0.01)	0.31 0.06)*	0.28 (0.04)#@	0.31 (0.06)*	0.28 (0.04)#@
p		0.656	**<0.0001**	**0.001**	**<0.0001**	**0.001**
PaO2/FiO2	**Survived**	237.8 (65.4)	386.8 (64.6)	398.0 (63.1)	397.2 (57.2)	397.0 (58.1)
	Died	251.0 (67.4)	333.1 (59.5)	373.2 (77.4)	403 (65.1)	340.5 (65.2)
p		0.658	0.069	0.392	0.825	**0.035**
MvO2	**Survived**	65.6 (6.6)	64.1 (4.1)	65.6 (3.3)	67 (3.7)	67.6 (4.1)
	Died	66.3 (4.9)	67.1 (4.1)	65.9 (4.2)	57.1 (4.1)	54.9 (4.3)
p		0.815	0.11	0.843	**<0.0001**	**<0.0001**
Qs/Qt	**Survived**	30.1 (3.9)	19.9 (3.0)	18.3 (3.7)	18.0 (3.4)	18.1 3.0)
	Died	27.8 (5.1)	23.7 (3.7)	18.9 (4.1)	21.3 (3.9)	25.0 (3.6)
p		0.201	**0.006**	0.723	**0.035**	**<0.0001**

*-p<0.05 as compared to T0, # - p<0.05 as compared to T0, @ - p<0.05 as compared to T0
Data are presented as mean (SD)
CI- cardiac index, CVP-central venous pressure, FiO2-fraction of inspired oxygen, MAP-mean arterial pressure, MPAP-mean pulmonary artery pressure, MVO_2- mixed venous oxygen saturation, PaO_2- partial pressure of oxygen, PCWP- pulmonary capillary wedge pressure, PVRI- pulmonary vascular resistance index, Qs/Qt- pulmonary shunt fraction, SPAP-systolic pulmonary artery pressure, SVRI-systemic vascular resistance index, TPG- transpulmonary gradient

Three types of acute RV dysfunction can develop after cardiac surgery based on severity:
1) Mild RV dysfunction without hemodynamic compromise.
2) Acute RVF resulting in difficulty separation from CPB.
3) Acute RVF causing low cardiac output syndrome.
Studies have reported ~75% mortality with acute perioperative RVF (27-30). Patients with severe MS, with tricuspid regurgitation and RV dysfunction preoperatively are prone to develop RV dysfunction after weaning from CPB. In our study, thirty-two patients (21.3%) with preexisting TR and RV dysfunction developed postoperative RV dysfunction. Six patients had developed acute RV failure and 5 out of these six (83.3%) patients died postoperatively. Therefore, prevention of acute postoperative RVF is critical (12, 13, 19, 20). Our results show that inhaled milrinone is superior to intravenous milrinone in preventing perioperative exacerbation of PAH and reducing the incidence and severity of acute RV failure. In our study, only 10.7% patients in iMil group developed RV dysfunction after surgery compared to 32% patients in IVMil group. Further, only 1 patient (1.3%) developed acute RV failure in iMil group compared to 5 patients (6.7%) in IVMil group. Inhaled milrinone acts by reducing the endothelial dysfunction, mitigation of free radical injury, uniform reduction of RV afterload and avoidance of ventilation-perfusion mismatch (20, 26). We believe that apart from the route, timing of inhaled milrinone delivery is also very crucial i.e., just before sternotomy and just before the termination of CPB. It is well proven that the effect of inhaled milrinone persists for only 20-30 min after the cessation of its inhalation. However, milrinone inhalation prior to sternotomy helps in the uniform distribution of the drug that stays in the lungs for a whole duration of CPB due to lack of significant perfusion. The second dose just after the removal of aortic cross-clamp supplements the action of first dose in effectively preventing the exacerbation of PH and precipitation of RVF (12).

Table 7. Follow-up data in iMIL and iVMIL groups

Variables	Group iMil (n=74)	Group IV Mil (n=71)	p
Follow-up duration, month	33.5 (4.2)	32.7 (4.4)	0.264
NYHA class, n(%) 1	60 (81.1)	57(80.3)	
2	10 (13.5)	11 (15.5)	
3	2 (2.7)	1 (1.4)	0.941
4	2 (2.7)	2 (2.8)	
Transthoracic echocardiography			
TR, n(%) Nil	65 (87.83)	61 (85.91)	
Mild	5 (6.75)	6 (8.45)	
Moderate	3 (4.05)	2 (2.81)	0.875
Severe	1 (1.35)	2 (2.81)	
TAPSE, mm	17.3(2.5)	18.1(3.1)	0.088
RVFAC, %	39.2(3.3)	38.7(4.1)	0.419
RV dysfunction, n(%)	6 (8.11)	8 (11.26)	0.519
LVEF, %	53.8(4.6)	55.1(4.0)	0.072
Outcomes, n(%)	4 (5.40)	4 (5.63)	0.949
Type of complication, n(%)			
Mitral prosthesis thrombosis, n(%)	2 (2.70)	1 (1.63)	0.583
Neurological complications, n(%)	1 (1.35)	1 (1.63)	0.974
Congestive heart failure, n(%)	2 (2.70)	3 (4.22)	0.615
Reoperation/ re-intervention, n(%)	2 (2.70)	1 (1.63)	0.583
Death, n(%)	3 (4.05)	3 (4.22)	0.956

Data are presented as mean (SD) and n(%)
LVEF- left ventricular ejection fraction, RV – right ventricular, RVFAC – right ventricular fractional area change, TAPSE - tricuspid annular plane systolic excursion, TR – tricuspid regurgitation

We also observed that immediate post CPB, deterioration of RV echocardiography parameters were more significant in IVMil group compared to iMil group. This finding denotes that inhaled milrinone is superior in preserving RV function compared to iv milrinone. Other studies have also reported the deterioration in the RV parameters early after surgery despite the hemodynamic improvement with iv pulmonary vasodilators (31). Further, as shown in ours, studies have reported that all the echocardiography parameters improved in majority who survived more than 48 hours after surgery (12, 31, 32). However, patients who died, these parameters had deteriorated remarkably early after surgery and failed to improve postoperatively. In our study also, we found that patients who died had marked deterioration in their hemodynamic and right ventricular echocardiographic parameters and difference became further significant at 48 hours after surgery. Due to the unpredictable course of pre-existing PAH, we believe it is better to preempt the onset of acute RV failure with inhaled milrinone or other inhalational rather than treating it later.

Systemic vascular resistance index is a marker of vascular tone and decrease in SVRI results in vasoplegia. In patients undergoing cardiac surgery, vasoplegia is common and usually transient after weaning from CPB. However, some patients may develop vasoplegia syndrome characterized by profound hypotension, SVRI <1600 dynes-sec/cm5/m2, normal or increased cardiac output, blunted or absent response to the fluid administration and need for non-catecholamine vasopressors to maintain the blood pressure. Patients with vasoplegia syndrome, who continue to be hypotensive despite the high doses of vasopressors have a poor prognosis, with 30-day all-cause mortality as high as 50%- 90% (33, 34). Pathophysiology of vasoplegia syndrome is incompletely understood. Milrinone being a vasodilator further aggravates the vasoplegia syndrome if administered systemically.

The same is shown by our results. In our study, 18 out of 22 patients who developed vasoplegia syndrome after weaning from CPB received intravenous milrinone. In our study, 4 patients in iMil group also develop vasoplegia syndrome suggesting other unknown factors may also be responsible for it. Further, all 5 patients who died in our study had SVRI <1600 dynes-sec/cm5/m2 at all time-point after weaning from CPB despite addition of vasopressor. These findings emphasize that inhalational milrinone instead of intravenous milrinone should be used to prevent the increase in PAP pressure and vasoplegia after weaning from CPB.

Our follow-up data showed that patients who survived the early postoperative period to discharge had 95.9% survival at 33.2 (4.1) months and >95% patients were NYHA class I/II irrespective of type of pulmonary vasodilator used. Right ventricular function improved to normal in echocardiography in 90.4% patients and only 3 patients (2.1%) developed severe tricuspid regurgitation. Further, complications (5.5%) and mortality (4.1%) remained low and comparable in both the groups. These findings suggest that if patients with severe MS who have severe PAH are managed appropriately and preemptively with inhalational milrinone in the perioperative period, they can have excellent survival with good quality of life.

Study limitations

Our study has few limitations. First, it was non-randomized study; therefore, there are chances of bias in patient selection. Second, we administrated milrinone inhalation with oxygen which itself can also reduce the PAP. Further, both our groups received milrinone infusion after surgery that may confound with results.

Conclusions

Inhalational milrinone is superior compared to intravenous milrinone in preventing postoperative acute right ventricular failure leading to decrease in morbidity and mortality. Patients who survive the early postoperative period, have excellent survival with good functional outcome and improvement in RV function. It should be used routinely in patients with severe MS associated with severe PAH and undergoing mitral valve replacement.

Ethics: Study was approved by the Ethics committee of our institute (UNMICRC/C.ANESTHESIA/2017/02), and written informed consent was obtained from all participants.

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Clinical studies	✓	✓		✓	
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