A prospective randomized comparative study between two different milrinone regimens in adult patients with pulmonary hypertension undergoing cardiac surgery

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Context
Milrinone is an inodilator commonly used to improve myocardial function and to decrease pulmonary hypertension.
Aim
The aim of this study was to compare two different regimens of milrinone administration in adult cardiac surgery patients with pulmonary hypertension.
Setting and design
A prospective, randomized, comparative study was conducted in Madinah Cardiac Center, Almadinah Almonourah, Saudi Arabia.
Material and methods
The study included 100 adult patients undergoing cardiac surgery with mean pulmonary artery pressure greater than 25 mmHg, as estimated preoperatively by Doppler echocardiography. The patients were classified randomly into two groups (n = 50): group A and group B. In group A, milrinone was started by infusion at a rate of 0.5 μg/kg/min without a loading dose at the beginning of CPB and continued postoperatively at a rate of 0.5–0.75 μg/kg/min in the cardiac surgical ICU. In group B, milrinone was given as a loading dose of 50 μg/kg over 10 min before weaning from CPB followed by infusion at a rate of 0.5–0.75 μg/kg/min postoperatively in the cardiac surgical ICU.
Statistical analysis used
Data were statistically described in terms of mean ± SD or frequencies and percentages, when appropriate, using the paired t-test.
Measurements and main results
Early milrinone using significantly decreased pulmonary artery pressure and pulmonary and systemic vascular resistances; it increased the right ventricular fractional area change, cardiac index, and urine output; and it decreased the serum lactate, pharmacological and mechanical supports, and ICU and hospital length of stay ($P < 0.05$).
Conclusion
The early administration of milrinone in adult cardiac surgery was associated with better hemodynamic effect, and it decreased the need for pharmacological supports. In addition, it was associated with shorter ICU and hospital length of stay without any side effects related to milrinone.

Keywords:
adult patients, cardiac surgery, cardiopulmonary bypass, milrinone, pulmonary hypertension

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Introduction

Pulmonary circulation is the major determinant of right ventricular afterload and right ventricular ejection fraction [1]. Several preoperative conditions increase the risk of developing perioperative pulmonary hypertension, including pre-existing pulmonary hypertension, mitral stenosis or regurgitation, and left ventricular dysfunction [2,3], and it may be aggravated by the release of vasoactive substances during cardiopulmonary bypass (CPB) [4–6].

The acute increase in right ventricular afterload results in an increase in the right ventricular end-diastolic volume, a decrease in the right ventricular ejection fraction, a decrease in the left ventricular end-diastolic volume with septal shift to the left and ballooning of the right ventricle, which can decrease cardiac output and right ventricular dysfunction [7]. Right ventricular dysfunction after CPB carries a poor prognosis, with a perioperative mortality ranging from 44 to 86% [8].

Milrinone is a type III phosphodiesterase inhibitor that increases the intracellular concentration of cyclic adenosine monophosphate in vascular smooth muscle cells and cardiomyocytes [9]. The effects of intravenous milrinone include pulmonary vasodilatation, systemic

vasodilatation, and increased inotropic effect [10]. The aim of this study was to compare two different regimens of milrinone administration in patients with pre-existing pulmonary hypertension and right ventricular dysfunction undergoing cardiac surgery.

Patients and methods

After obtaining informed consent and approval of the local ethics and research committee at Madinah Cardiac Center, Almadinah Almonourah, Saudi Arabia (2012–2013), a prospective randomized study was conducted including 100 adult patients undergoing cardiac surgery with mean pulmonary artery pressure more than 25 mmHg, as estimated preoperatively by Doppler echocardiography. The pulmonary was secondary to left-side heart diseases (aortic valve regurge, mitral valve stenosis or regurge, or ischemic cardiomyopathy). We excluded patients with acute myocardial infarction within the previous 8 weeks, active myocarditis, malfunctioning artificial heart valve, obstructive cardiomyopathy, pericardial disease, primary pulmonary disease, renal impairment, hepatic impairment, or thyroid disease. The patients were classified by simple randomization into two groups (n = 50 in each group).

Group A: Milrinone was started as an infusion at a rate of 0.5 μg/kg/min at the beginning of CPB, and it was continued postoperatively (0.5–0.75 μg/kg/min) in the adult cardiac surgical ICU (CSICU). The perfusionists were informed at the beginning of administration of milrinone to observe the mean arterial blood pressure during CPB.

Group B: Milrinone was started as a loading dose of 50 μg/kg over 10 min before weaning from CPB and continued as an infusion (0.5–0.75 μg/kg/min) postoperatively in the adult CSICU. The infusion rate of 0.5–0.75 μg/kg/min was used, as it is the most common standard rate used to produce plasma levels of milrinone at 100–300 ng/ml to manage cardiac patients with pulmonary hypertension [11,12].

Monitoring of patients

Hemodynamic monitoring consisted of heart rate, mean arterial blood pressure, central venous pressure, mean arterial pulmonary pressure, pulmonary capillary wedge pressure, pulmonary and systemic vascular resistances, cardiac index, serum lactate level, urine output, and mixed venous oxygen saturation. Derived cardiovascular variables, namely cardiac index and pulmonary and systemic vascular resistances, were calculated using standard formulae, and the measurements were based on the bolus thermodilution technique using the mean of three consecutive 10-ml injectates of 5% glucose through the pulmonary artery catheter. Hemodynamic values were serially collected at the following time points: at baseline, after induction of anesthesia; 10 min after weaning of CPB, at the end of surgery; on admission to the ICU; and 6 and 24 h after ICU admission.

After induction, a transesophageal echocardiography probe was inserted to obtain a standard sequence of cardiac images during a period of hemodynamic stability before pericardiotomy and again after sternal closure. Baseline and postoperative values were obtained by cardiologists. Global right ventricular systolic function was evaluated by measuring the fractional area change, which is equal to the difference between the end-diastolic and end-systolic area divided by the end-diastolic area obtained in the four-chamber view. In addition, transesophageal echocardiography assessed the left ventricular and valvular functions.

Anesthetic technique

For all patients, and under local anesthesia, a radial arterial cannula, central venous line, and a pulmonary artery catheter (Arrow International Inc. USA) were inserted before operation to enable continuous hemodynamic monitoring. Induction was done by intravenous fentanyl (3–5 μg/kg), etomidate (0.3 mg/kg), and rocuronium (0.8 mg/kg). The anesthesia was maintained with oxygen, sevoflurane (1–3%), fentanyl infusion (1–3 μg/kg/h), and cisatracurium (1–2 μg/kg/min). CPB was established with cannulation of the ascending aorta and right atrium, and the anesthesia was maintained by fentanyl and propofol infusion (1–3 mg/kg/h) during CPB. At the end of surgical intervention, the patients were prepared for weaning from CPB. In addition to the milrinone, and if there was difficulty to wean from CPB, pharmacological support (dopamine or epinephrine or norepinephrine or nitroglycerine) or mechanical support [intra-aortic balloon pump (IABP)] was started. At the end of the surgery, the patients were transferred to CSICU with full monitoring.

Statistical analysis

Data were statistically described in terms of mean ± SD, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's t-test for independent samples. Within-group comparison of numerical variables was done using paired t-test. For comparing categorical data, χ^2-test was performed. Exact test was used instead when the expected frequency is less than 5. P-value less than 0.05 was considered to be statistically significant. All statistical calculations were performed using computer programs SPSS version 15 for Microsoft Windows (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA).

Results

Table 1 shows no statistical difference between the two groups for age, weight, sex, ejection fraction of patients, history of hypertension, diabetes mellitus, and Euroscore of patients ($P > 0.05$) (Table 1). The weaning from CPB was easier in group A patients than in group B patients. Patients of group A needed smaller doses of pharmacological support (dopamine, epinephrine, norepinephrine, and nitroglycerine) than patients of group B ($P < 0.05$) (Table 2), and the requirement for mechanical support (IABP) was higher in patients of group B compared with those of group A, but it was statistically insignificant ($P > 0.05$) (Table 2). The total milrinone dose was significantly higher in group A patients than in group B patients before weaning from CPB ($P = 0.031$), but the comparison was insignificant after weaning from CPB ($P = 0.548$), and in the ICU ($P = 0.736$) (Table 2).

Table 3 shows the hemodynamics of the patients before and after starting the study medication; there was no difference regarding the heart rate, mean arterial blood pressure, central venous pressure, and mixed venous oxygen saturation ($P > 0.05$) (Table 3). The mean arterial pulmonary blood pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, and systemic vascular resistance decreased significantly after the weaning from CPB, and the decrease was more in group A patients than in group B patients ($P < 0.05$) (Table 3). The fractional area change of the right ventricle increased significantly in patients of group A, with minimal changes in patients of group B, and the comparison between the two groups was significant ($P < 0.05$) (Table 3). The cardiac index increased in patients of both groups after CPB, but the increase was more in group A patients than in group B patients ($P < 0.05$) (Table 3). The urine output increased after CPB to a greater extent in group A patients than in group B patients ($P < 0.05$) (Table 3). In comparison with preoperative levels, the serum lactate level increased greatly after CPB in patients of group B, with minimal change in group A patients, and also the comparison between the two groups after CPB was significant ($P < 0.05$) (Table 3). Table 4 shows that the ICU and Hospital lengths of stay were prolonged with late milrinone using ($P = 0.039$, $P = 0.023$ respectively). There are two mortality cases with early milrinone group and three cases with late milrinone using and the comparison was statistically insignificant ($P = 1.000$).

Discussion

This study compared two different regimens of milrinone administration in adult patients with severe pulmonary hypertension undergoing cardiac surgery. The weaning of patients from CPB was easier in the early milrinone group than in the late milrinone group, and the patients needed smaller doses of pharmacological support (dopamine, epinephrine, norepinephrine, and nitroglycerine) and less mechanical support (IABP) compared with the late milrinone group. The study showed that mean arterial pulmonary blood pressure and pulmonary vascular resistance decreased significantly with early use of milrinone at the beginning of CPB compared with conventional

Table 1 Preoperative data of patients

Items	Group A ($n = 50$)	Group B ($n = 50$)	*P*-value
Age (years)	52.54 ± 10.15	51.86 ± 8.75	0.719
Weight (kg)	81.12 ± 9.27	81 ± 11.58	0.954
Sex			
Female	22	24	0.572
Male	28	26	0.641
DM	25	23	0.689
Hypertension	19	22	0.542
Ejection fraction (%)	34.64 ± 7.21	35.62 ± 7.23	0.499
Euroscore	11.19 ± 2.87	11.58 ± 3.01	0.547
Body surface area (m^2)	1.76 ± 0.16	1.76 ± 0.15	0.431
CABG	21	19	0.683
Valvular surgery	12	9	0.461
CABG + valvular surgery	17	22	0.305

Data are presented as mean ± SD or number; CABG, coronary artery bypass grafting; DM, diabetes mellitus.

Table 2 Intraoperative data of patients

Items	Group A ($n = 50$)	Group B ($n = 50$)	*P*-value
CPB time (min)	129.50 ± 23.97	128.60 ± 19.87	0.838
Cross-clamping time (min)	111.06 ± 12.22	110.40 ± 10.85	0.775
IABP	6	8	0.564
Pacing	4	6	0.739
Dopamine (μg/kg/min)	5.25 ± 1.43	8.12 ± 1.50	0.036*
Epinephrine (μg/kg/min)	0.07 ± 0.05	0.11 ± 0.06	0.016*
Norepinephrine (μg/kg/min)	0.02 ± 0.02	0.05 ± 0.03	0.023*
Nitroglycerine (μg/kg/min)	0.51 ± 0.03	0.92 ± 0.13	0.035*
Milrinone dose (mg)			
Before weaning	6.26 ± 1.12	4.15 ± 0.75	0.031*
After weaning	6.71 ± 0.75	6.85 ± 0.93	0.548
ICU	148.01 ± 16.68	148.70 ± 19.26	0.736

Data are presented as mean ± SD or number; Before weaning: the total milrinone dose before weaning from CPB; after weaning: the total milrinone dose after weaning from CPB to end of surgery; ICU: the total milrinone dose until discontinuation of milrinone; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; *$P < 0.05$: the comparison is significant between the two groups.

Table 3 Hemodynamics of patients

Items	Timing	Group A (n = 50)	Group B (n = 50)	P-value
Heart rate (bpm)	Pre	86.4 ± 10.98	85.72 ± 9.53	0.741
	Post	90.18 ± 7.58	89.72 ± 7.26	0.717
MAP (mmHg)	Pre	92.82 ± 6.38	93.08 ± 6.73	0.843
	Post	94.16 ± 6.68	94.34 ± 7.43	0.899
CVP (mmHg)	Pre	12.38 ± 1.99	12.46 ± 2.26	0.852
	Post	12.34 ± 1.88	12.20 ± 2.12	0.728
mPAP (mmHg)	Pre	30.90 ± 6.74	29.74 ± 5.91	0.362
	Post	21.44 ± 2.97†	23.78 ± 3.17†	0.001*
PCWP (mmHg)	Pre	21.18 ± 2.37	20.90 ± 2.71	0.583
	Post	17.84 ± 1.75†	17.64 ± 2.26†	0.022*
SVR (dyne/s/cm^5)	Pre	1307.50 ± 128.61	1305.7 ± 126.02	0.945
	Post	944.9 ± 124.59†	1042.3 ± 126.02†	0.001*
PVR (dyne/s/cm^5)	Pre	422.80 ± 94.23	433.3 ± 99.26	0.588
	Post	287.40 ± 21.80†	316.04 ± 21.20†	0.001*
RV FAC (%)	Pre	29.06 ± 3.20	28.80 ± 2.96	0.588
	Post	43.64 ± 3.65†	34.28 ± 3.51†	0.001*
Cardiac index (l/min/m^2)	Pre	2.02 ± 0.13	2.01 ± 0.14	0.836
	Post	2.97 ± 0.35†	2.30 ± 0.21†	0.001*
SvO_2 (%)	Pre	78.90 ± 2.60	78.94 ± 3.50	0.948
	Post	80.40 ± 3.07	80.42 ± 3.88	0.977
Urine output (ml/kg/h)	Pre	1.36 ± 0.20	1.35 ± 0.18	0.959
	Post	2.78 ± 0.66†	1.88 ± 0.26†	0.001*
Serum lactate (mmol/l)	Pre	1.53 ± 0.26	1.54 ± 0.39	0.810
	Post	2.13 ± 1.15	4.78 ± 1.76†	0.016*

Data are presented as mean ± SD; CVP, central venous pressure; MAP, mean arterial blood pressure; mPAP, mean pulmonary arterial blood pressure; PCWP, pulmonary capillary wedge pressure; Post, the values after medication study administration; Pre, the values before medication study administration; PVR, pulmonary vascular resistance; RV FAC, right ventricular fractional area change; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance; *P < 0.05: the comparison is significant between the two groups; †P < 0.05: the comparison is significant before and after milrinone administration within the same group.

administration of milrinone before the weaning from CPB. In addition, the right ventricular fractional change area increased significantly with early use of milrinone. The decrease in right ventricular afterload and increased contractility result in the improvement of the right ventricular systolic function. The decrease in systemic vascular resistance and positive inotropic effect of milrinone result in a significant increase in cardiac index with early use of milrinone. Early milrinone was infused without the bolus dose to avoid the possible problems such as hypotension related to bolus administration, and we found clinically that the early milrinone is more effective than the late milrinone with the bolus dose. The total milrinone dose given before weaning from CPB was higher in patients in the early milrinone group, and this may be related to the improvement of outcomes with early milrinone administration.

A similar study was conducted in pediatric patients. The study involved 40 pediatric patients undergoing congenital corrective cardiac surgery and classified randomly into two groups (n = 20): patients of one group received milrinone infusion (0.5 μg/kg/min) without a loading dose at the beginning of CPB and continued postoperatively (0.5–0.75 μg/kg/min) in the pediatric CSICU, and the other group received milrinone at a loading dose of 50 μg/kg over 10 min after CPB weaning and continued as infusion (0.5–0.75 μg/kg/min) postoperatively in the pediatric CSICU. The weaning from CPB was easier with early milrinone, and the need for pharmacological and mechanical support was lower with early milrinone than with late milrinone. The mean arterial blood pressure through the first 6 h after CPB, SvO_2, and urine output was significantly higher in the early milrinone group in comparison with the late milrinone group. The serum lactate level was also lower with early milrinone than with late milrinone (P < 0.05) [13].

A retrospective analysis on high-risk patients included 73 patients with a mean preoperative Parsonnet score of 27 ± 14. Inhaled milrinone (5 mg) was administered before or after CPB. The patients who received milrinone before CPB initiation were weaned easily from CPB (P = 0.02); the pulmonary artery pressure decreased after CPB (P = 0.01) and there was significant improvement of ventricular function. In addition, the rate of IABP insertion decreased as compared with that with administration after CPB, and the mortality incidence between the two was

insignificant. No detectable side effects were directly linked to the administration of the drug [14].

Baruch *et al*. [15] found that continuous infusion of milrinone without a loading dose improved hemodynamic and positive inotropic effects to a greater extent in patients with decompensated heart failure who underwent right heart catheterization compared with patients who received continuous infusion initiated with a bolus. They measured plasma milrinone levels serially over 24 h; the plasma concentration of a continuous infusion without a bolus reached the same level after 1 h as the concentration in patients who received continuous infusion initiated with a bolus, and the same results were found by other studies [16,17].

The present study showed that infusion of milrinone at the beginning of CPB as in group A has a potent vasodilator effect and may be associated with improving tissue perfusion, as indicated by lower serum lactate levels, higher urine output, and normal mixed venous oxygenation, compared with usual administration of milrinone as in group B, which can be explained by the study conducted by Möllhoff and colleagues. They evaluated the effects of milrinone on splanchnic oxygenation in patients undergoing coronary artery bypass grafting, and they found that milrinone improved splanchnic perfusion in patients undergoing routine coronary artery bypass grafting [18], and that it also increased the postoperative oxygen transport to tissue after cardiac surgery by increasing cardiac output [19].

Many studies found that milrinone causes smooth muscle relaxation and vasodilatation in addition to a positive inotropic effect. These effects result in decreases in systemic vascular resistance, central venous pressure, and pulmonary artery occlusion pressure, as well as increases in stroke volume and cardiac output owing to afterload reduction, and improvement of right ventricular function by decreasing the pulmonary vascular resistance [20–24].

Study limitations

There are two limitations to this study: first, the serum level of milrinone was not measured, as the kits for measurement were not available in the laboratory, and second the study populations of the this study were small.

Table 4 Postoperative outcome of patients

Items	Group A (n = 50)	Group B (n = 50)	P-value
ICU length of stay (days)	5.96 ± 3.09	7.38 ± 3.68	0.039*
Hospital length of stay (days)	15.00 ± 4.36	18.12 ± 4.83	0.023*
Mortality	2	3	1.000

Data are presented as mean ± SD or number; *P < 0.05: the comparison is significant between the two groups.

Conclusion

In this study, early milrinone using significantly decreased pulmonary hypertension, increased right ventricular fractional area change, increased cardiac index, facilitated weaning from CPB, decreased the postoperative pharmacological and mechanical supports, and decreased the ICU and hospital length of stay to a greater extent than late milrinone in adult patients with pulmonary hypertension who underwent cardiac surgery without any side effects related to milrinone.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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