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ORIGINAL RESEARCH

Comparison of Inhaled and Intravenous Milrinone in Patients with Pulmonary Hypertension Undergoing Mitral Valve Surgery

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ABSTRACT

Introduction: Increased pulmonary vascular resistance (PVR) is detrimental to cardiac output in postoperative cardiac-surgery patients. The aim of this study was to investigate the postoperative hemodynamic effects of milrinone inhalation, and determine whether it has a selective effect of pulmonary vasodilation in patients with pulmonary hypertension undergoing mitral valve replacement surgery. ***Methods:*** In this study, 48 patients with pulmonary hypertension who underwent mitral valve replacement surgery were included. Patients were randomly divided into two groups with 24 patients in each: the inhaled group and the control group (intravenous [i.v.] milrinone). In the inhaled group, milrinone was administered with a jet nebulizer, and nebulized for 4 hours. In the control group, patients received a bolus of 50 μg/kg i.v. milrinone, then received a continuous milrinone infusion, 0.5 μg/kg/min, for 4 hours. A number of hemodynamic changes in all patients were evaluated. ***Results:*** With milrinone administration, mean pulmonary artery pressure (MPAP) and PVR showed a comparable decrease in both groups. However, after initiation of milrinone, both mean arterial pressure and systemic vascular resistance in the inhaled group were significantly higher than in the control group. MPAP and PVR returned to baseline values 60 minutes after termination of milrinone inhalation. In addition, in the inhaled group, there was a reduction in intrapulmonary shunt fraction (Qs/Qt), with an improvement in PaO_2/FiO_2 (arterial oxygen tension/fraction of inspired oxygen). ***Conclusion:*** The major advantage of inhaled milrinone is its pulmonary selectivity, thereby avoiding systemic side effects and ventilation-perfusion mismatch. Inhaled milrinone is an effective pulmonary vasodilator and appears to be an alternative promising approach in addressing the problem of right-ventricular decompensation following cardiopulmonary bypass.

Keywords: cardiopulmonary bypass; inhaled milrinone; mitral valve surgery; pulmonary hypertension; pulmonary vascular resistance

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INTRODUCTION

Patients with pulmonary hypertension (PHT) are at substantially increased risk of perioperative morbidity and mortality after cardiac surgery.[1] It has been suggested that up to 58% of early postoperative mortality is associated with PHT.[2] PHT is a frequent and serious complication of mitral valve disease, resulting from elevated left atrial pressure. It is frequently seen in patients with mitral valve disease, and may be aggravated by endothelial dysfunction related to cardiopulmonary bypass-associated lung injury after mitral valve replacement surgery.[3]

PHT can be treated with intravenous (i.v.) vasodilators, but such therapy is frequently limited by systemic vasodilation and hypotension. Agents that produce selective pulmonary vasodilation by lowering pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), but without affecting systemic vascular resistance (SVR), are of special clinical interest in the setting of cardiothoracic anesthesiology. Recent research has been directed towards inhalation as a route for the treatment of PHT, as well as the introduction of new techniques to optimize drug delivery. Inhaled vasodilators may circumvent potentially deleterious systemic side effects by acting predominantly on the pulmonary circulation.[4,5]

The phosphodiesterase inhibitor milrinone is usually preferred in patients with PHT and myocardial dysfunction after cardiopulmonary bypass.[6] This study was undertaken to determine whether inhaled aerosolized milrinone has a selective effect of pulmonary vasodilation in patients with PHT after mitral valve replacement.

MATERIALS AND METHODS

The protocol of this study was reviewed and approved by the ethics committee of Zhejiang University, and informed consent was obtained from all patients. Patients with PHT (mean PAP [MPAP] >25 mmHg)[7] scheduled to undergo mitral valve replacement surgery by cardiopulmonary bypass were enrolled in this study from January 1, 2007 to December 1, 2008, from the Second Affiliated Hospital, Zhejiang University, China. Of these patients, 48 fulfilled the following inclusion criteria: postoperative PVR >200 dyn·s/cm^5 and postoperative MPAP >25 mmHg; both measurements were obtained twice within a 30-minute period. The following exclusion criteria were used: patients who had an emergency operation, thromboembolic disease treated with anticoagulant therapy (ie, patients with a history of pulmonary embolism and not isolated deep venous thrombosis), severe renal or liver dysfunction, coagulopathy, or thrombocytopathy. Patients were randomly divided into two groups with 24 patients in each, by using sealed envelopes; the inhaled group receiving inhaled milrinone, and the control group receiving i.v. milrinone.

Anesthesia was induced with etomidate, midazolam, sufentanil, and rocuronium, and all patients were ventilated with 100% inspired oxygen. Anesthesia was maintained with a continuous infusion of propofol during the operation. All patients were monitored intraoperatively and postoperatively with a Swan-Ganz catheter and an arterial pressure line.

The study was performed in the immediate postoperative period, in the cardiothoracic intensive care unit. All patients were mechanically ventilated with 40% inspired oxygen, and sedated with propofol or the combination of fentanyl with propofol. In the inhaled group, milrinone was administered with a jet nebulizer (Micro Mist Nebulizer model A4002; Yuque Inc., Nanjing, China) attached to the inspiratory limb of the ventilator circuit, just before the Y-piece, approximately 10 cm proximal to the endotracheal tube. The mean mass diameter of particles

delivered by this nebulizer from aqueous solution is 2.0 μm at a rate of approximately 6 mL/h. The concentration of milrinone used in the inhaled group was 1 mg/mL (dissolved in dextrose); patients received inhaled milrinone for 4 hours. In the control group, patients received a bolus of 50 μg/kg i.v. milrinone, then received a continuous milrinone infusion, 0.5 μg/kg/min for 4 hours.

Hemodynamic parameters recorded included: heart rate (HR), mean arterial pressure (MAP), MPAP, cardiac index, SVR, and PVR. Arterial and mixed venous blood samples were taken during each assessment point and immediately analyzed by the Stat Profile-M (Nova Biomedical, Boston, MA, USA). The evaluation of mixed venous oxygen saturation (SvO_2), intrapulmonary shunt fraction (Qs/Qt), and arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2) ratio were all calculated by standard formulas.[8]

Statistical procedures were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean±SD. The groups were compared by means of analysis of variance for repeated measurements (RMANOVA) with the within-group factor time and the between-group factor treatment (inhaled milrinone vs. i.v. milrinone). Where there were significant differences between the groups, post-hoc testing was performed using the Tukey-HSD test. A value of $P<0.05$ was considered to be significant.

RESULTS

Demographic data for the inhaled milrinone and control groups are described in Table 1. There were no significant differences in age, gender, weight, or height ($P>0.05$).

In the inhaled group, all patients tolerated inhaled milrinone without any side effects. In the control group, systemic hypotension (MAP <60 mmHg) occurred and lasted more than 5 minutes in two patients during the period of i.v. milrinone. However, this difference in incidence of hypotension (0/24 vs. 2/24 in inhaled and control groups, respectively) during milrinone administration was not significant ($P=0.148$).

Effects of inhaled milrinone and i.v. milrinone on systemic and pulmonary hemodynamics in patients with PHT are shown in Table 2. Before milrinone administration, both groups were comparable with respect to systemic and pulmonary hemodynamics. In both groups, MPAP and PVR showed a comparable decrease following milrinone administration. However, after 2-4 hours of milrinone administration, both MAP and SVR in the inhaled group were significantly higher than in the control group ($P<0.05$). MPAP and PVR returned to baseline values 60 minutes after withdrawal of milrinone inhalation. Conversely, HR did not change throughout the procedure in both groups

Table 1. Patient demographics.

	Inhaled group (n=24)	**Control group (n=24)**	***P* value**
Age, years	43.35±8.63	49.87±10.36	0.372
Weight, kg	66.24±8.15	63.3±10.21	0.521
Height, cm	167.6±12.30	163.9±11.65	0.475
Gender, male/female	10/14	11/13	0.771

All data presented as mean±SD.

Table 2. Effects of inhaled milrinone (n=24) and intravenous milrinone (n=22) on systemic and pulmonary hemodynamics in patients with pulmonary hypertension.

		T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8
HR, bpm	Inhaled	76.3±8.1	72.3±10.2	77.8±7.9	80.5±9.6	76.8±7.4	74.9±9.7	78.7±10.2	82.6±10.5	81.4±9.6
	Control	78.4±9.3	75.2±11.4	76.9±8.6	74.5±8.9	74.5±9.1	77.3±10.2	81.2±9.3	78.6±8.7	76.7±10.1
MAP, mmHg	Inhaled	82.6±12.3	77.9±16.6	78.8±13.1	81.7±12.2†	82.2±13.5†	79.4±16.8	80.5±13.3	77.4±15.6	82.5±14.9
	Control	77.9±11.6	75.3±14.3	73.5±11.1	73.7±9.9	73.2±10.9	81.3±12.8	81.6±12.2	79.7±13.2	78.6±11.8
MPAP, mmHg	Inhaled	36.9±8.9	29.9±7.3*	28.6±8.2*	29.5±7.8*	28.3±6.8*	30.3±8.7*	30.9±7.8*	31.6±8.6*	35.3±9.2
	Control	33.6±7.8	28.1±7.7*	26.9±7.8*	30.2±8.3*	28.7±7.6*	31.6±9.2*	32.6±9.4	32.9±8.3	33.1±8.4
CI, L/min/m^2	Inhaled	2.5±0.3	2.9±0.6*	3.0±0.7*	3.0±0.7*	3.2±0.8*	2.9±0.5*	3.1±0.7*	3.2±0.6*	3.2±0.7*
	Control	2.6±0.4	2.8±0.9	3.1±0.9*	3.1±0.6*	2.9±0.8*	3.1±0.6*	3.0±1.0*	3.2±0.8*	3.1±0.5*
PVR, dyn·s/cm^5	Inhaled	673±141	345±96*	365±88*	402±102*	386±92*	378±86*	423±108*	454±116*	572±132
	Control	701±152	462±102*	379±102*	413±79*	376±86*	386±93*	453±121*	479±122*	563±109
SVR, dyn·s/cm^5	Inhaled	2309±407	2110±429	1968±394†	2232±431†	1987±387†	2108±369	1928±454	2249±371	2009±357
	Control	2529±513	1735±289	1372±267	1345±263	1432±237	1809±324	2021±423	2039±382	2110±342
PaO_2/FiO_2	Inhaled	224.3±56.3	332.5±63.5*†	324.5±75.6*	394.1±63.9*†	362.2±73.8*	374.3±92.3*†	364.2±56.3*	344.9±83.5*	369.2±78.8*
	Control	233.6±62.3	242.2±58.3	263±50.9	241.2±71.3	279.6±59.3	267.3±71.6	279.5±61.9	301.5±71.4*	312.6±67.3*
Qs/Qt, %	Inhaled	23.9±6.4*	18.6±5.6*†	17.1±6.6*†	18.3±7.4*	17.5±6.4*	16.1±7.2*	18.5±6.9*	19.1±7.3*	19.3±11.3
	Control	21.9±7.3	22.6±6.2	21.4±5.4	21.9±6.4	20.6±7.2	18.6±7.9	19.2±7.1	18.2±6.7	19.0±8.2
SvO_2, %	Inhaled	63.8±4.3	62.5±3.6	65.8±4.5	65.4±5.3	63.4±5.7	62.9±5.1	63.7±4.8	65.2±4.4	62.7±3.9
	Control	66.0±5.1	63.7±4.6	64.3±6.2	64.9±5.5	62.9±7.1	63.5±7.0	64.6±5.3	63.7±5.6	63.8±4.7

NB: In inhaled group, n=22 as two patients were hypotensive and were not included.

*P<0.05 compared to baseline; †P<0.05 compared to control group.

CI=cardiac index; HR=heart rate; MAP=mean arterial pressure; MPAP=mean pulmonary artery pressure; PaO_2/FiO_2=arterial oxygen tension/fraction of inspired oxygen; PVR=pulmonary vascular resistance; Qs/Qt=intrapulmonary shunt fraction; SvO_2=venous oxygen saturation; SVR=systemic vascular resistance; T_0=before milrinone administration, baseline; T_1=1 hour after start of milrinone administration; T_2=2 hours after start of milrinone administration; T_3=3 hours after start of milrinone administration; T_4=4 hours after start of milrinone administration; T_5=15 minutes after end of milrinone administration; T_6=30 minutes after end of milrinone administration; T_7=45 minutes after end of milrinone administration; T_8=60 minutes after end of milrinone administration.

(P>0.05). Cardiac index increased throughout the course of milrinone administration in both groups, and remained significantly higher than baseline 60 minutes after the end of milrinone inhalation (P<0.05). Inhaled milrinone increased the PaO_2/FIO_2 ratio from the beginning of inhalation to the end of the 5-hour observation time (P<0.05). In addition, inhaled milrinone also decreased the Qs/Qt ratio during the same period (P<0.05). However, these effects were not observed in the control group with respect to the PaO_2/FIO_2 ratio and the Qs/Qt ratio. There were no statistically significant differences at any time with respect to SvO_2 (P>0.05).

DISCUSSION

The results of this study demonstrate that the application of inhaled milrinone produces a significant reduction in PVR in patients after mitral valve operations, without reducing SVR.

In patients undergoing mitral valve replacement surgery, pre-existing PHT is often aggravated due to a variety of pathophysiologic processes.[3] Both ischemia-reperfusion injury of the pulmonary vascular endothelium, and the activation of inflammatory and vasoconstrictor cascades may result in exacerbation of pre-existing PHT.[3] Several days or even weeks might be required for the increased PVR to return to normal after the valve replacement.[9] PVR is the primary determinant of right-ventricular afterload, and increased PVR may lead to right-ventricle failure.[10] Therefore, during the immediate postoperative period it is important to use a pulmonary vasodilator to keep PVR within the limits that allow the right ventricle to work.

Intravenous administration of vasodilators, such as nitroglycerin, sodium nitroprusside, phentolamine, and milrinone, all produce pulmonary vasodilation. However, the use of these agents may be limited by systemic vasodilation and hypotension. Furthermore, i.v. vasodilators produce pulmonary vasodilation in both the ventilated and nonventilated alveoli, leading to an increased intrapulmonary shunt fraction, and hence, hypoxemia.[11] In contrast, administering vasoactive agents by the inhalation route, so that vasodilation is confined to pulmonary circulation, may reduce the incidence of these side effects. Clinical strategies used via the inhalation route to treat PHT include nitric oxide, milrinone, and a prostacyclin analog.[4,5,12]

Inhaled aerosolized milrinone has been shown to act as a selective pulmonary vasodilator without systemic effects, in patients with both primary and secondary PHT.[13-15] As the duration of pulmonary vasodilatory effects of inhaled milrinone after the withdrawal of inhalation is short (no more than 30 minutes), continuous administration appears to be required.[13,15] However, no data are available regarding the continuous administration of inhaled milrinone for more than 60 minutes in postoperative cardiac-surgery patients with PHT. In addition, inhaled milrinone produces vasodilation of pulmonary vasculature adjacent to well-ventilated alveoli, increases blood flow to these areas, and preferentially shunts blood away from poorly ventilated regions;[16] thus, it matches ventilation/perfusion and reduces intrapulmonary shunt. This results in improved oxygenation and reduced PVR and right-ventricular afterload.

To our knowledge, this is one of the longest durations of treatment with inhaled milrinone reported to date. In this study, both pulmonary and systemic hemodynamic responses to inhaled milrinone were also measured, to give further insight into the potential role of this

agent in managing patients with PHT after mitral valve replacement. After milrinone inhalation, as our results demonstrated, selective pulmonary vasorelaxation was achieved, with MPAP and PVR values decreasing significantly. Conversely, MAP and SVR values were not affected. In control patients a significant decrease was observed after administration of milrinone, suggesting that inhaled milrinone is selectively targeting the pulmonary circulation. Our results have shown that 60 minutes after termination of 4-hour inhalation of milrinone, both MPAP and PVR returned to baseline. This contrasts with the Haraldsson et al. study, which found that the duration of pulmonary vasodilatory effects following a 15-minute inhalation of milrinone was only 20 minutes.[13] Thus, in the present study we have shown that continuous milrinone inhalation may prolong the duration of pulmonary vasodilation.

A limitation of the study is that in the inhaled group, the exact dose of milrinone reaching the alveolar space cannot be determined because of losses in the nebulizer chamber, ventilator, and endotracheal tubing.[17] Furthermore, alveolar deposition of aerosols during mechanical ventilation has been estimated to be 6%-10% of the nominal dose placed in the nebulizer.[17] In this study, both i.v. and inhaled milrinone showed no side effects; it may be that the study was too small to determine whether inhaled milrinone reduces other side effects associated with i.v. milrinone administration.

CONCLUSION

Inhaled milrinone is an effective pulmonary vasodilator and seems to be a promising alternative approach in addressing the problem of postcardiopulmonary bypass right-ventricular decompensation. The major advantage of inhalation therapy is the combined beneficial effects of milrinone with its pulmonary selectivity, thereby avoiding systemic side effects and ventilation-perfusion mismatch. However, long-term benefits of inhaled milrinone in relation to improved outcome remains to be studied. Inhalation of milrinone is a less expensive, straightforward, and effective alternative[14] for PHT therapy when compared with i.v. administration.

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