Original Article

Randomized Comparative Study of Intravenous Infusion of Three Different Fixed Doses of Milrinone in Pediatric Patients with Pulmonary Hypertension Undergoing Open Heart Surgery

Neeraj Kumar Barnwal, Sanjeeta Rajendra Umbarkar, Manjula Sudeep Sarkar, Raylene J Dias[1]

Departments of Cardiac Anesthesiology and [1]Pediatric Anesthesiology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

Abstract

Background: Pulmonary hypertension secondary to congenital heart disease is a common problem in pediatric patients presenting for open heart surgery. Milrinone has been shown to reduce pulmonary vascular resistance and pulmonary artery pressure in pediatric patients and neonates postcardiac surgery. We aimed to evaluate the postoperative outcome in such patients with three different fixed maintenance doses of milrinone. **Methodology:** Patients were randomized into three groups. All patients received fixed bolus dose of milrinone 50 μg/kg on pump during rewarming. Following this, patients in low-dose group received infusion of milrinone at the rate of 0.375 μg/kg/min, medium-dose group received 0.5 μg/kg/min, and high-dose group received 0.75 μg/kg/min over 24 h. Heart rate, mean arterial pressure (MAP), mean airway pressure (MaP), oxygenation index (OI), and central venous pressure (CVP) were compared at baseline and 24 h postoperatively. Dose of inotropic requirement, duration of ventilatory support and Intensive Care Unit (ICU) stay were noted. **Results:** MAP, MaP, OI, and CVP were comparable in all three groups postoperatively. All patients in the low-dose group required low inotropic support while 70% of patients in the high-dose group needed high inotropic support to manage episodes of hypotension (P = 0.000). Duration of ventilatory support and ICU stay in all three groups was comparable (P = 0.412, P = 0.165). **Conclusion:** Low-dose infusions while having a clinical impact were more beneficial in avoiding adverse events and decreasing inotropic requirement without affecting duration of ventilatory support and duration of ICU stay.

Keywords: *Congenital heart disease, milrinone, pulmonary hypertension*

Introduction

Pulmonary hypertension (PHT) is failure of systemic oxygenation because of marked pulmonary arterial hypertension secondary to elevated pulmonary vascular resistance (PVR) or altered pulmonary vasoreactivity. This may lead to extrapulmonary shunting (right to left) of blood across foramen ovale, the patent ductus arteriosus, atrial septal defects, and ventricular septal defects. PHT secondary to congenital heart defects such as ventricular septal defect is a common problem with significant morbidity and mortality.

Phosphodiesterase (PDE) III and V are enzymes that inactivate cyclic adenylate monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), respectively, the principal second messengers of nitric oxide and prostacyclins. Thus, the PDE inhibitors: sildenafil, vardenafil, and milrinone, act to augment cAMP- and cGMP-mediated actions, leading to vasodilation and decreased PVR.

Milrinone, a selective inhibitor of PDE III in cardiac myocytes and vascular smooth muscle, not only acts similarly to the PDE V inhibitors but also acts as a positive inotrope and has been shown to reduce PVR and pulmonary artery pressure (PAP) in experimental models of PHT in adult humans and neonates postcardiac surgery.[1,2] Effects of bolus infusion followed by variable dose maintenance infusion have been studied in the adult population.[3]

We aimed to evaluate the postoperative outcome in pediatric patients having congenital heart disease and PHT with three different fixed maintenance doses of intravenous (IV) milrinone. Our primary outcome measures were to study the effects of three different fixed maintenance doses

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Address for correspondence:
Dr. Neeraj Kumar Barnwal, 2/7, Stone Building, B. J. Marg, Byculla, Mumbai - 400 011, Maharashtra, India.
E-mail: docneerajbarnwal@gmail.com

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of IV milrinone on heart rate (HR), mean arterial pressure (MAP), mean airway pressure (MaP), oxygenation index (OI), and central venous pressure (CVP) of pediatric patients having congenital heart disease with severe PHT, and secondary outcome measures were to study dose of inotropic requirement, duration of ventilatory support and ICU stay in each group.

We hypothesized that milrinone even at low maintenance doses (0.375 μg/kg/min) would have a similar effect on oxygenation, MaP, and thus, PVR compared to the medium-dose (0.5 μg/kg/min) and high-dose (0.75 μg/kg/min) infusions.

Methodology

We conducted a prospective randomized double-blind study in a single center on a total of ninety patients. Institutional Review Board approval and written informed parental consent for the study were obtained. Children of either sex between 6 weeks and 12 years of age of American Society of Anesthesiology physical status II or III having congenital heart disease with severe PHT posted for open heart surgery were included in the study. Severe PHT was defined as mean PAP >50 mmHg measured by pulmonary regurgitant jet on preoperative color Doppler echocardiography. Children having persistent primary PHT (presenting with PHT within 6 weeks of age), PHT with reversal of shunt (Eisenmenger syndrome), dextrocardia, and congestive cardiac failure were excluded from the study. The patients were divided into three groups of thirty pediatric patients in each group by computerized random number generated table: Group 1 (low-dose group), Group 2 (medium-dose group), and Group 3 (high-dose group). In all three groups, anesthesia was induced with sevoflurane, intravenous (IV) midazolam 0.1 mg/kg, and IV fentanyl 5–10 μg/kg followed by muscle relaxation with IV rocuronium 1.2 mg/kg. The airway was secured with appropriate size endotracheal tube. Internal jugular vein and arterial cannulation were done. Anesthesia was maintained with isoflurane between 1 and 1.2 minimum alveolar concentration and infusion of midazolam 0.05 mg/kg/h, fentanyl 2 μg/kg/h, and vecuronium 0.04 mg/kg/h. Monitoring included HR, oxygen saturation, invasive as well as noninvasive blood pressure, end-tidal carbon dioxide, arterial blood gas, CVP, nasopharyngeal, and rectal temperature. Following institution of cardiopulmonary bypass (CPB), perfusion pressure was maintained between 35 and 45 mm of Hg with moderate hypothermia. All patients received fixed bolus dose of milrinone 50 μg/kg on pump during rewarming (34°C). Following this, different fixed dose IV infusion of milrinone was started while the patients came off CPB. This infusion was prepared by the investigators, and the infusion pump was labeled only with the drug name but not dose. Thus, the observer recording the findings was not aware of the infusion dosages. In Group 1 (low-dose group [n = 30]) - patients received continuous IV infusion of milrinone at the rate of 0.375 μg/kg/min. In Group 2 (medium-dose group [n = 30]) - patients received continuous IV infusion of milrinone at the rate of 0.5 μg/kg/min. In Group 3 (high-dose group [n = 30]) - patients received continuous IV infusion of milrinone at the rate of 0.75 μg/kg/min. At all-time points, continuous beat-to-beat hemodynamic monitoring was done in all patients. Inotropes were started (dopamine and/or adrenaline as per institutional protocol for pediatric cardiac surgical patients) if systolic blood pressure (SBP) fell below the 5th percentile for age and if started was continued for 24 h in all patients.

Following parameters were compared after induction of general anesthesia, and 24 h after shifting the patient to ICU: (1) HR (beats/min) (2) MAP (mmHg) (3) MaP (mmHg) (4) OI = $FiO_2 \times MaP/PaO_2$, FiO_2 = fraction of inspired oxygen, MaP (mmHg), PaO_2 (mmHg) = partial pressure of oxygen in arterial blood and (5) CVP (cm H_2O). We also recorded duration of patient on ventilator (12–24 h, >24 h up to 48 h, >48 h), length of ICU stay (<48 h, 48–72 h, >72 h), and dose of inotropic requirement in all three groups (low dose [only dopamine <10 μg/kg/min or dopamine <10 μg/kg/min and adrenaline <0.05 μg/kg/min]; high dose [dopamine ≥10 μg/kg/min and adrenaline ≥0.05 μg/kg/min]).

Milrinone infusion was terminated in all patients after 24 h of shifting to ICU, in those patients who developed hypotension (SBP <5th percentile for age) which could not be managed by standard inotropic infusion (dopamine at 5–20 mcg/kg/min and/or adrenaline at 0.02–0.2 mcg/kg/min) and in patients who developed hemodynamically unstable arrhythmia which could not be controlled by standard measures. Adverse effects of milrinone such as hypokalemia, arrhythmia, and bronchospasm were looked for and if occurred were treated appropriately. Withdrawal criteria for the study were unable to wean from CPB, termination of milrinone before 24 h due to the above-mentioned adverse effects, or death of the patient within 24 h of the surgical procedure.

Statistics

Sample size of 88 was estimated based on study between two different milrinone regimens in adult patients with PHT undergoing cardiac surgery[4] where mean HR in Group 1 was 90.18 ± 7.58 and Group 2 was 89.72 ± 7.26. With type 1 error at 5% level of significance and 80% power of the study, we used sample size calculation for three groups. We took a total of 90 patients to compensate for possible loss of data.

The results were analyzed using computer generated software SPSS version 16 (SPSS Inc., Chicago, Illinois, USA). Quantitative data are presented with the help of mean, standard deviation. Mean difference in values of HR, MAP, MaP, and OI from postinduction to 24 h

after shifting to ICU was calculated in each of the three groups. This mean difference between the three groups was compared with the help of ANOVA. Mean difference in CVP in each of the three groups from postinduction to 24 h after shifting to ICU was calculated with the help of Kruskal–Wallis test. Pearson's Chi-square test was used as test of significance to find out association for qualitative data (requirement of inotropic support [high vs. low], duration of patient on ventilator, and length of ICU stay). $P < 0.05$ was considered statistically significant.

Results

There were no major protocol violations or severe adverse drug effects, and data of all ninety patients enrolled in the study were included in the analysis. The age, sex, weight distribution of patients, and surgical procedures performed are depicted in Table 1. All three groups were comparable for age and weight [Table 1]. The mean difference in HR from after induction to 24 h after shifting to ICU was statistically significant in all three groups (P = 0.009) [Table 2]. The mean difference in MAP from after induction to 24 h after shifting to ICU was comparable in all three groups.(P = 0.357) [Table 2]. The mean difference in MaP from after induction to 24 h after shifting to ICU was comparable in all three groups (P = 0.171) [Table 2]. The mean difference in OI from after induction to 24 h after shifting to ICU was comparable in all three groups (P = 0.29) [Table 2]. The mean difference in CVP was comparable in all three groups (2.43 ± 1.25 in Group 1, 2.70 ± 0.95 in Group 2, and 2.90 ± 0.48 in Group 3; P = 0.403) [Table 2]. In Group 1, all 30 (100%) patients required low inotropic support. In Group 2, 23 (76.7%) patients needed low inotropic support, and 7 (23.3%) patients needed high inotropic support. In Group 3, 9 (30%) patients needed low inotropic support while 21 (70%) needed high inotropic support [Figure 1].

Table 1: Patient baseline characteristics (n=90)

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)
Demographics			
Age, years (mean±SD)	1.650±1.71	2.650±1.12	1.36±1.71
Weight, kg (mean±SD)	9.583±2.95	8.767±2.07	9.600±3.02
Male	18	13	17
Female	12	17	13
Surgery (n=90)			
Repair of VSD (n=66)	22	22	22
Repair of TAPVC (n=14)	4	5	5
Repair of DORV (n=7)	4	-	3
Repair of PAPVC (n=2)	-	2	-
Repair of CAVC (n=1)	-	1	-

VSD: Ventricular septal defect, TAPVC: Total anomalous pulmonary venous connection, DORV: Double outlet right ventricle, PAPVC: Partial anomalous pulmonary venous connection, CAVC: Complete atrioventricular canal, SD: Standard deviation

This difference in inotropic requirement between the three groups was statistically significant (P = 0.000). In all three groups, 45 patients required ventilatory support for >24–48 h, 33 patients required support for 12–24 h while only 12 required support for >48 h [Table 3]. The duration of ventilatory support between all three groups was comparable (P = 0.412) [Table 3]. Forty-three patients required ICU stay for >48–72 h, 35 required ICU stay for <48 h, and only 12 needed ICU stay for >72 h [Table 4]. The duration of ICU stay between all three groups was comparable (P = 0.165) [Table 4].

Discussion

PHT is frequently associated with pediatric patients having congenital heart disease and results in significant perioperative morbidity and mortality. It can produce a low cardiac output syndrome (LCOS) which affects nearly 25% of neonates and young children after cardiac surgery.[5,6]

Milrinone is a PDE III inhibitor which induces pulmonary vasodilatation by its actions through a cAMP-mediated signaling pathway. It increases cardiac output, reduces systemic and PVR, and decreases filling pressures.[1,2] It has proven beneficial hemodynamic effects in patients with congestive cardiac failure and in patients with low output states following cardiac surgery.[7] Our primary outcome measures were to study the effects of three different fixed maintenance doses of IV milrinone on HR, MAP, MaP, OI, and CVP of pediatric patients having congenital heart disease with severe PHT, and secondary outcome measures were to study dose of inotropic requirement, duration of ventilatory support and ICU stay in each group.

Parameters such as MAP, MaP, OI, and CVP showed no significant difference (P = 0.357 for MAP, P = 0.171 for MaP, P = 0.29 for OI, P = 0.40 for CVP) between Group 1, Group 2, or Group 3 patients. Thus, a low maintenance dose (0.375 µg/kg/min) of milrinone was as effective as medium- and high-dose infusion in improving MAP, MaP, OI, and thus decreasing PVR. Although HR

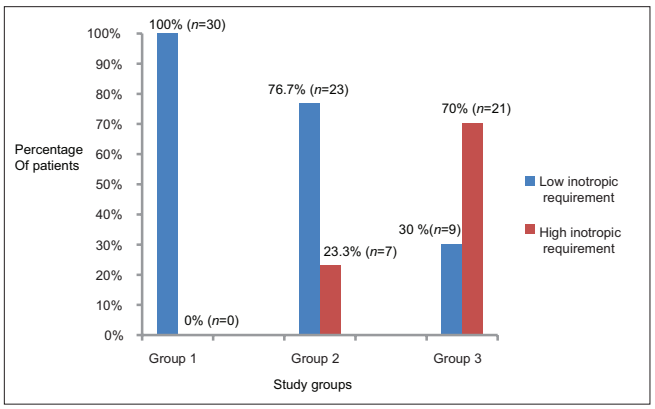

Figure 1: Comparison among three groups for the inotropic requirement. Group 1: Low-dose milrinone group, Group 2: Medium-dose milrinone group, Group 3: High-dose milrinone group

Table 2: Difference between study parameters from after induction to 24 h after shifting to Intensive Care Unit

Group (*n*=30)	Mean±SD		Mean difference±SD	*P*
	After induction	After 24 h		
HR				
Group 1	120.17±5.025	121.17±3.582	−1.00±3.60	0.009
Group 2	121.8±5.365	120.07±5.132	1.73±4.45	
Group 3	122±4.785	122.93±3.183	−0.93±3.27	
MAP				
Group 1	81.3±4.348	81.37±3.2	−0.07±3.32	0.357
Group 2	78.53±4.539	79.53±3.137	−1.00±3.64	
Group 3	77.27±2.258	78.33±1.583	−1.07±1.64	
CVP				
Group 1	6.233±0.6261	3.533±0.6288	2.70±0.95	0.403
Group 2	6.133±0.8604	3.7±0.8367	2.43±1.25	
Group 3	6.233±0.4302	3.333±0.5467	2.9±0.48	
MaP				
Group 1	8.2±0.407	6.1±0.305	2.100±0.403	0.171
Group 2	8.47±0.507	6.23±0.43	2.233±0.504	
Group 3	8.13±0.346	6.1±0.305	2.033±0.320	
OI				
Group 1	6.0733±0.2947	3.113±0.4637	2.96±0.48	0.287
Group 2	6.4017±0.29139	3.677±1.0248	2.72±0.95	
Group 3	5.9933±0.09444	3.043±0.3380	2.95±0.33	

Data significant at $P<0.05$. *P* values are for intergroup comparisons. HR: Heart rate, MAP: Mean arterial pressure, CVP: Central venous pressure, MaP: Mean airway pressure, OI: Oxygenation index, SD: Standard deviation, Group 1: Low-dose group, Group 2: Medium-dose group, Group 3: High-dose group

Table 3: Comparison between study groups for duration of patient on ventilator

Group	Duration on ventilator			*P* (Pearson Chi-square test)
	12-24 h	>24-48 h	>48 h	
Group 1 (*n*=30)	10	16	4	0.412
Group 2 (*n*=30)	15	11	4	
Group 3 (*n*=30)	8	18	4	
Total (*n*=90)	33	45	12	

Data significant at $P<0.05$. *P* value is for intergroup comparison. Group 1: Low-dose group, Group 2: Medium-dose group, Group 3: High-dose group

Table 4: Comparison between study groups for length of Intensive Care Unit stay

Group	Length of ICU stay			*P* (Pearson Chi-square test)
	<48 h	48-72 h	>72 h	
Group 1 (*n*=30)	10	16	4	0.165
Group 2 (*n*=30)	15	9	6	
Group 3 (*n*=30)	10	18	2	
Total (*n*=90)	35	43	12	

Data significant at $P<0.05$. *P* values are for intergroup comparisons. Group 1: Low-dose group, Group 2: Medium-dose group, Group 3: High-dose group, ICU: Intensive Care Unit

changes in each of the three groups were statistically significant ($P = 0.009$), this did not translate into clinically significant difference evident from the mean values of HR 24 h after shifting to ICU in the three groups [Table 2].

The episodes of hypotension during perioperative period were managed by dopamine or combination of dopamine and adrenaline. The need for high inotropic requirement was statistically significant in Group 3 patients whereas all patients in Group 1 needed low inotropic support ($P = 0.000$). Due to the vasodilatory properties of milrinone, the systemic vascular resistance decreases in a dose-dependent manner. Hence, at higher doses, there can be profound hypotension requiring high inotropic support.

Low maintenance doses (0.375 μg/kg/min) of milrinone had a similar effect on duration of ventilatory support ($P = 0.412$) and length of ICU stay ($P = 0.165$) compared to medium- and high-dose infusions.

There were no severe adverse events such as ventricular or supraventricular tachycardia, hypokalemia in either of the groups. This may be attributed to the fact that these side effects are seen infrequently in the pediatric population as compared to adult patients.[8]

To the best of our knowledge, there is no study which has compared these three different doses of milrinone on PVR in pediatric patients having preexisting severe PHT undergoing congenital heart surgery. The PRIMACORP trial (PRophylactic Intravenous use of Milrinone After Cardiac OpeRation in Pediatrics)[8] to assess efficacy and safety of milrinone in preventing LCOS in infants and children after corrective surgery for congenital

heart disease, represents the largest randomized trial in a pediatric cardiac surgical population reported in literature. The authors reported 25.9% patients in the placebo group, 17.5% in the low-dose group (25 μg/kg bolus over 60 min followed by a 0.25 μg/kg per min infusion for 35 h), and 11.7% in the high-dose group (75 μg/kg bolus followed by a 0.75 μg/kg per min infusion for 35 h) experienced LCOS. The study showed a 64% relative risk reduction in the development of LCOS with the prophylactic use of high-dose milrinone and a statistically insignificant trend in patients treated with low-dose milrinone. There were no significant differences in the incidence of hypotension or duration of ventilatory support with either dose of milrinone. They concluded that use of high-dose milrinone after pediatric congenital heart surgery reduces the risk of LCOS. The results of our study add controversy to this evidence. However, there was no mention of the status of PHT in the patients before surgery in the PRIMACORP study, whereas in our study, all patients having severe PHT were included. Variations in the definitions of low-dose and high-dose infusions preclude comparisons between the two studies.

In a study to evaluate the hemodynamic effects of IV milrinone in neonates with low cardiac output after cardiac surgery,[1] authors reported results similar to that of our study. Milrinone administered as a bolus of 50 μg/kg over 15 m followed by an infusion rate of 0.5 μg/kg/m for 30 m was effective in reducing systemic and PVR while improving cardiac index.

It is our anecdotal opinion that decreased inotropic requirement associated with the use of low-dose milrinone infusion (0.375 μg/kg/min) may reduce overall treatment cost by decreasing morbidity related to high inotropic support. This may be important in policy making in centers having a huge turnover of critical pediatric cardiac surgical cases, especially children with severe PHT.

There were a few limitations to this study. We analyzed hemodynamic data only at two points of time, namely, induction of general anesthesia and 24 h after shifting to ICU. Although measurements were done more frequently, only these two time points were chosen for analysis to compare patient outcome at 24 h from baseline. Had we analyzed data more frequently we may have got different findings. Direct PVR measurement was not performed as pulmonary artery catheters were not inserted due to practical problems in using them in very small babies. PVR was extrapolated from CVP, MaP, and OI. Direct PVR measurements with the insertion of pulmonary artery catheters or surgically placed pulmonary artery line for direct pressure measurement and postoperative monitoring could be the subject for a future extended study.

Conclusion

The use of low-dose maintenance infusion of milrinone (0.375 μg/kg/min) was equally effective as medium- and high-dose infusions on hemodynamics, OI, PVR, duration of ventilatory support, and length of ICU stay in children with severe PHT undergoing congenital heart surgery. Effects such as hypotension which occurred more frequently with high-dose infusions requiring high inotropic support were not seen with low-dose infusions. We believe that low-dose infusions while having a clinical impact are more beneficial in avoiding adverse events and decreasing inotropic requirement without affecting the duration of ventilatory support and ICU stay.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Chang AC, Atz AM, Wernovsky G, Burke RP, Wessel DL. Milrinone: Systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. Crit Care Med 1995;23:1907-14.
2. Bailey JM, Miller BE, Lu W, Tosone SR, Kanter KR, Tam VK. The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. Anesthesiology 1999;90:1012-8.
3. Wright EM, Skoyles J, Sherry KM. Milrinone in the treatment of low output states following cardiac surgery. Eur J Anaesthesiol Suppl 1992;5:21-6.
4. Soliman R, Atta RA. A prospective randomized comparative study between two different milrinone regimens in adult patients with pulmonary hypertension undergoing cardiac surgery. Egypt J Cardiothorac Anesth 2014;8:91-6.
5. Parr GV, Blackstone EH, Kirklin JW. Cardiac performance and mortality early after intracardiac surgery in infants and young children. Circulation 1975;51:867-74.
6. Wernovsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR, *et al*. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 1995;92:2226-35.
7. Feneck RO. Intravenous milrinone following cardiac surgery: I. Effects of bolus infusion followed by variable dose maintenance infusion. The European Milrinone Multicentre Trial Group. J Cardiothorac Vasc Anesth 1992;6:554-62.
8. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, *et al*. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107:996-1002.