The early use of milrinone in arterial switch operations for patients with transposition of the great arteries

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Citation

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Abstract

Background. During the arterial switch operation the left ventricle is acutely converted from the pulmonary to the systemic ventricle. This imposes a significant increase in after load on the left ventricle and may predispose the patient to acute left ventricle dysfunction in the immediate post-operative period. Milrinone improves myocardial contractility, diastolic relaxation and decrease in after load due to vasodilatation. We conduct this study to determine the effects of milrinone infusion on hemodynamic profile in pediatric cardiac surgery.

Methods. This is double prospective, randomized, controlled study. 14 patients were randomized to receive either (group B) milrinone infusion 0.25ug/Kg/min immediately after induction , to be followed by 0.5ug/Kg/min at 10 minutes post release of the cross-clamp (7 patients) and the second group (group A) they going to receive a bolus dose of 50ug/Kg (10 min post release of cross-clamp) to be followed by 0.5ug/Kg/min as infusion (7 patients). Data collected were: left atria pressure (LAP), central venous pressure (CVP), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate(HR) (immediately after off -pump, 30 minutes post-bypass and 60 minutes post- bypass and after chest sternum closure) for the arterial switch operation in neonates and infants.

Results. The primary end point for efficacy evaluation was based on the haemodynamic profile where (group A) they received loading dose of milrinone followed by infusion of milrinone, which resulted in decrease of left atrial pressure (LAP), while in (group B) milrinone infusion was started at induction of anesthesia and was resulted in decrease of central venous pressure (CVP).

Conclusions. After switching in neonates and infants milrinone bolus dose followed by milrinone infusion was shown to be more effective on a post-bypass course of homodynamic profile by decreasing the LAP.

INTRODUCTION

Congenital cardiovascular defects can cause abnormal patterns of blood flow and influence structural and functional circulatory development. Advances in cardiac surgery – including improved cardiopulmonary bypass (CPB), post-operative care and repair of complex cardiac defects – have made surgical repair a primary therapy for an increasing number of paediatric patients with cardiovascular disease.[1] The causes of low cardiac output after cardiac surgery are multifactorial. After surgery there are acute changes in the loading conditions of the myocardium. Surgical repair of cardiac malformation exposes the myocardial tissue to prolonged periods of myocardial ischaemia[1] and cardioplegia[2]. Residual lesions, even if minor (e.g. tricuspid regurgitation) may complicate the physiologic mechanisms. Finally, some repairs require a ventriculotomy for adequate surgical exposure and repair which may result in myocardial dysfunction. CPB causes activation of the inflammatory cascade, with secondary elevations of systemic and pulmonary vascular resistance. Capillary leak and pulmonary dysfunction and the ability to achieve a rapid haemodynaic response after intravenous administration of Milrinone is extremely important after separation from CPB, where uncompensated low cardiac output syndrome (LCOS) can soon result in deterioration of the patient's haemodynamic status and subsequent secondary organ dysfunction[3]. Distinctly different from Digitalis, Glycosides or Catecholamine's, Milrinone is a bipyridine compound that selectively inhibits PDE III cyclic adenosine monophosphate (CAMP) isozyme, causing CAMP-mediated increases in

cardiac muscle contractile force and vascular muscle relaxation[4, 5,6]. The clinical utility of Milrinone in the paediatric population, therefore, is similar to that of Milrinone in adult patients with heart failure. Milrinone effectively improves cardiac index in adult patients with congestive heart failure[7] or LCOS occurring after cardiac surgery[8, 9].

The adverse effects of Milrinone are due to the high plasma level, decreasing systemic vascular resistance and venous return, especially in hypovolemic patients. Therefore, slower administration of Milrinone over a 10-15 minute period is recommended. Like other inotropes, it has a pro-arrhythmic effect. None of the research authors found any significant changes in platelet number or function in the paediatric cardiac surgical population requiring cardiopulmonary bypass, beyond the usual adverse effects of a cardiac surgical procedure and cardiopulmonary bypass on platelets.

During the arterial switch operation the left ventricle is acutely converted from the pulmonary to the systemic ventricle. This imposes a significant increase in after load on the left ventricle and may predispose the patient to acute left ventricular dysfunction in the immediate post-operative period. Even in patients who appear to be doing well clinically there is often a decrease in cardiac index over the first 8-24 hours following surgery[10]. Clinically Milrinone improves myocardial contractility, diastolic relaxation and causes a decrease in after load through vasodilatation, therefore, increases cardiac index and lower left ventricular filling pressure after cardiopulmonary bypass, even in comparison to inotropes or vasodilators[11]. The aim of this study was to evaluate the effects of milrinone on hemodynamic profile in pediatric surgical patients.

PATIENTS & METHODS

After approval of the Research and Ethics Committee of the hospital we conducted a double, prospective, randomized, controlled study to definitively determine if early start of milrinone as infusion after the induction of anaesthesia makes a difference in the haemodynamic profile of the left atrial pressure (LAP), central venous pressure (CVP), systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) that at off pump, 30 min, 60 min post-bypass and after closure of the sternum. Before induction of anaesthesia non-invasive monitoring (ECG, SPO2) were placed. After induction of anaesthesia invasive monitoring (Arterial line, CVP line) were inserted and connected. LAP line was inserted by the Surgeon before coming off the bypass. 14 patients undergoing neonatal and infant arterial switch operation. Patients were randomized to receive either group B (7 patients) milrinone infusion 0.25ug/kg/min. immediately after induction of anaesthesia and to be followed by 0.5ug/kg/min at 10 minutes after release of the cross-clamp. Group A (7 patients) will receive a bolus dose of Milrinone 50ug/kg (10 minutes post release of the cross-clamp) and to be followed by Milrinone infusion with a dose of 0.5ug/kg/min. CPB time, aortic cross-clamp time, were noted intraoperative.Also complications like death were also noted. Data were analyzed using student-newman-keuls multiple comparison test of ANOVA, t-test for independent groups, fisher exact test and Pearson correlation coefficient.

RESULTS

There were no significant differences among the two groups with respect to any of the patient characteristics, as summarized in Table 1. The data of haemodynamic variables are shown in Table 2. The effects of milrinone for group A patients on left atrial pressures (LAP) were significantly lower than those of group B patients immediately after off-pump (P<0.001), 30 minute post off-pump (P<0.0001) and 60 minute post off-pump (P<0.0001) Fig2. While the effects of milrinone for group A patients on central venous pressures (CVP) were significantly lower than those of group A patients after sternum closure (P<0.014). There were no significant differences among the two groups in the systolic blood pressure (SBP) and diastolic blood pressure (DBP) immediately post-off pump, 30 minutes, 60 minutes or after sternum closure. There was significant difference between the two groups in the heart rate post sternum closure (P<0.041). Intraoperative death was reported in one patient from group B.

Figure 1

Table 1: Demographic date

Parameter	Group	n	Mean value	SEM	p value
Age	B	7	17.143	±3.680	
	A	7	23.571	±4.163	ns
Weight	B	7	3.129	±0.193	
	A	7	3.414	0.187	ns

Figure 2

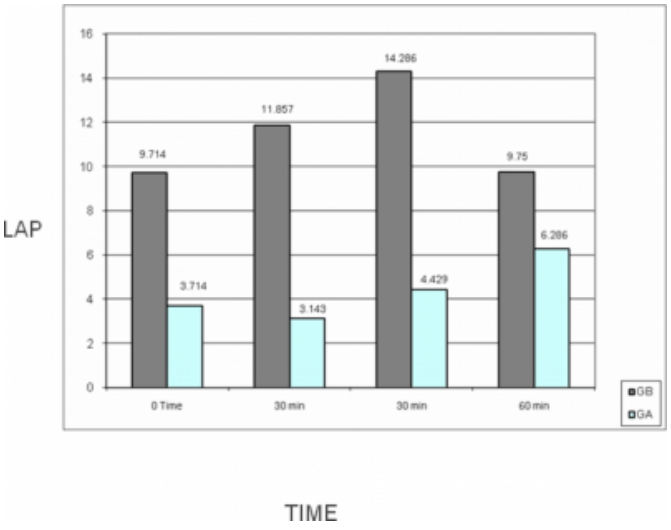
Table 2: Heamodynamic effects of Milrinone

	Study Group	N	Mean	Std Deviation	St Error Mean	P-Valve
Lap immediately after off-pump	B A	7 7	9.714 3.714	2.752 1.976	1.040 .747	0.001
Lap 30 min	B A	7 7	11.857 3.143	4.059 2.035	1.534 .769	<0.0001
Lap 60m	B A	7 7	14.286 4.429	2.059 1.512	.778 .571	<0.0001
Lap after sternal closure	B A	4 7	9.750 6.286	1.258 2.870	.629 1.085	0.051
cvp immediately post off-pump	B A	7 7	11.714 12.429	9.742 4.198	3.682 1.587	0.862
CVP 30 min	B A	7 7	10.143 12.143	7.946 1.345	3.003 .508	0.524
CVP 60 min	B A	7 7	10.857 14.000	6.890 2.160	2.604 .816	0.272
CVP after sternal closure	B A	4 7	9.750 16.000	2.062 3.742	1.031 1.414	0.014
SBP imm post off-pump	B A	7 7	71.429 76.143	6.477 6.517	2.448 2.463	0.2
SBP 30 min	B A	7 7	73.286 75.429	10.531 6.528	3.980 2.467	0.655
SBP 60 min	B A	7 7	71.143 78.000	10.653 11.475	4.026 4.337	0.269
SBP post-sternal closure	B A	4 7	71.500 79.143	7.188 8.454	3.594 3.195	0.164
DPB imm post off-pump	B A	7 7	46.714 43.000	8.958 3.651	3.386 1.380	0.330
DPB 30 min	B A	7 7	50.143 44.571	8.395 5.827	3.173 2.202	0.175
DPB 60 min	B A	7 7	51.286 47.429	11.265 8.600	4.258 3.250	0.485
DBP post-sternal closure	B A	4 7	46.750 50.143	3.948 6.176	1.974 2.334	0.354
HR imm post off-pump	B A	7 7	141.143 130.714	35.900 17.905	13.569 6.767	0.505
HR 30 min	B A	7 7	151.571 131.857	17.738 17.063	6.704 6.449	0.056
HR 60 min	B A	7 7	151.857 141.429	13.146 9.981	4.969 3.772	0.120
HR post-sternal closure	B A	4 7	164.75 144.29	18.21 10.70	9.10 4.05	0.041
CBP time	B A	7 6	223.00 178.50	77.60 7.58	29.33 3.10	0.181
Aortic cross-clamp time	B A	7 7	90.57 88.29	21.30 19.47	8.05 7.36	0.838

Abbreviations: A = group A, B = group B, LAP = Left Atrial Pressure, CVP = Central Venous Pressure; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Heart Rate CPB time = Cardiopulmonary bypass time (duration) ACC time = Cross Clamp time (duration).

Figure 3

Figure 1: Left Atrial Pressure of Milrinone for Group A and Group B



DISCUSSION

Cardiac output is one of the major components of oxygen delivery so that its maintenance is an important consideration. Due to pre-operative cardiac lesion and myocardial dysfunction secondary to the events related to cardiac surgery and cardiopulmonary bypass, circulatory supports by pharmacological means is frequently required. Therefore, inotropes and vasodilators are used to improve cardiac performance after cardiac surgery. Epinephrine, Dopamine and Dobutamine are commonly used inotropes; phosphodiasterase III inhibitors as Milrinone have been introduced in clinical practice recently. Milrinone produces a positive inotropic effect with concurrent vasodilatation and little chronotropic effect and lacking the undesirable effects of catecholamine which includes an increase in heart rate and myocardial oxygen consumption, down-regulation of beta-adrenergic receptors and increase in systemic vascular resistance. As a result of these differences milrinone has become a valuable tool in the treatment of infants and children following cardiac surgery. Several investigators have studied the effect of milrinone in reversing the low cardiac output frequently observed in infants and children after cardiac surgery (25% of cases develop low cardiac output syndrome after cardiac surgery). Chang and colleagues administered milrinone 50 mic.gm over 15 minutes in 10 neonates suffering from low output syndrome following cardiac surgery and observed an average increase in CI of 42% and average decrease in systemic and pulmonary vascular resistance of 37% and 27% respectively [12].

Baily et al characterized the pharmacodynamics of Mirinone along its correlation with the pharmacokinetics in 20 children between 3-22 months of age after they underwent repair of congenital heart defect. A loading dose of 50 mic.gm/kg given over a period of 5 minutes resulted in a mean decrease in mean arterial pressure of 12% and mean increase in cardiac index of 18% at a mean peak plasma concentration of 235 ngm/ml [13].

Chucc et al studied the effect of a loading dose of 20 mic.gm/kg followed by continuous infusion of 0.2 mic.gm/kg/min. in 10 children with post bypass pulmonary hypertension after TOF repair within 6 months, they found a significant reduction in PAP/SBP within 15 minutes and the effects persisted for 24 hours during infusion without remarkable adverse effects[14].

An important multicentre study done in the USA (31 centers participated in this study) evaluated the efficacy and safety of prophylactic Milrinone in pediatric patients (about 238 patients) at high risk for developing low cardiac output

syndrome, they used different doses of Milrinone and they concluded that high dose milrinone, after paediatric congenital heart surgery, reduce the risk of low cardiac output syndrome [15]. The anti-inflammatory capability of milrinone has been explored offering another potential mechanism of clinical efficacy [16].

It was proven in the previous and other studies that milrinone has a steady pharmacokinetic in children. Intravenous infusion of 2 doses of 25 mic.gm/kg bolus followed by infusion rate of 0.75 mic.gm/kg/min. achieved a plasma concentration of milrinone that between >100 ng/ml to 900 ng/ml, a level considered to be therapeutic in adult [17], [18].

In conclusion, we have found that bolus dose of milrinone 50ug/kg/min followed by 0.5ug/kg/mi as infusions significantly decrease the left atrial pressure in neonates and infants after switch surgery. we have also found that infusion dose of milrinone 0.25ug/kg/min immediately after induction of anesthesia followed by 0.5ug/kg/mi at 10minuts post release of cross-clamp significantly decrease CVP after sternum closure.

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