

Effects of early and late intravenous infusion of milrinone in children upto 1 year undergoing cardiac surgery-A comparative study

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Abstract :

Objective: To compare the effects of early and late use of milrinone in children up to 1 year undergoing complex cardiac surgery. **Study design:** prospective randomized study. **Methods:** A prospective study involved 30 children undergoing congenital corrective cardiac surgery, classified randomly into two groups. **Group A:** Milrinone infusion was started without loading dose at 0.5mcg/kg/min at the beginning of CPB and continued postoperatively (0.5-0.75 mcg/kg/min) in the paediatric cardiac surgical ICU. **Group B:** Milrinone was started as a loading dose of 50mcg/kg over 10 min after aortic declamping and continued as infusion postoperatively at 0.5-0.75 mcg/kg/min in the pediatric cardiac surgical ICU. Data were collected at baseline, 1st, 6th and 12th postoperative hours in the ICU. **Results:** The inotropic supports and mechanical supports were needed more in group B than group A. The comparison of heart rate, CVP were insignificant between the two groups ($P > 0.05$). The mean arterial blood pressure through the first 6 hours postoperatively was higher in group A than group B ($P < 0.05$), but became insignificant through other timepoints. The urine output and central venous oxygen saturation were higher in group A than group B ($P < 0.05$). The serum lactate levels were significantly higher in group B more than group A ($P < 0.05$). **Conclusion:** Early use of milrinone, lead to easy weaning from Cardiopulmonary bypass, decreased requirement of pharmacological and mechanical support and decreased incidence of low cardiac output syndrome after pediatric cardiac surgery and there was no complications related to milrinone in

our study patients.

Keywords : Cardiac surgery, Inotropes, Milrinone, Low cardiac output syndrome

Introduction :

Predictable fall in cardiac output has been documented in several studies, referred to as low cardiac output syndrome (LCOS), which occurs after congenital heart surgery. Cause of LCOS after cardiac surgery is myocardial ischaemia after aortic cord clamping.¹ Etiology of LCOS is left ventricular (LV) dysfunction, right ventricular (RV) or systemic ventricular (single ventricle anatomy) dysfunction and may include systolic or diastolic dysfunction. Medical management includes such as inotropes, steroids, inodilators, afterload reducing agents and mechanical ventilation used to initiate cardiac output thus decreasing oxygen demand and improving the oxygen supply to tissues. When medical interventions fail, switch to Extracorporeal Membrane Oxygenation (ECMO) to support end organ function, allowing for myocardial recovery.²

The key to reduce the LCOS is early recognition and timely intervention. Many physiologic, hemodynamic, and serologic variables can be assessed and re-assessed in order to diagnose LCOS. Both invasive and non-invasive monitoring strategies are used. It is important to appreciate that estimations of cardiac function, cardiac output and tissue oxygenation, based on the interpretation of findings of physical examination and hemodynamic parameters such as the central venous pressure, heart rate and blood pressure are often measured.³

Traditionally to enhance tissue perfusion and facilitate postoperative recovery inotropes and vasodilators are used. Drawbacks of use of catecholamines are increased myocardial oxygen consumption, increase heart rate, afterload and risk of arrhythmia. Because of these potential limitations, phosphodiesterase inhibitors such as amrinone and milrinone have been increasingly used in the postoperative period.⁴

Pharmacology of Milrinone:

Milrinone, is a phosphodiesterase-3 inhibitor with inodilating and lusitropic properties independent of alpha and beta receptors.

Mechanism of Action: Its direct myocardial effect is related to the increase in intracellular cyclic adenosine monophosphate with a simultaneous increase in intracellular calcium levels and increased sensitivity of

the actin–myosin complex to calcium which leads to increased myocardial contractility. Removal of calcium from cytosol by the sarcoplasmic reticulum is accelerated by concomitant activation of phospholamban by cyclic adenosin monophosphate thus shortening contraction time and leaving more time for myocardial relaxation in each cardiac cycle.^{5,6} The direct vasodilating effect on peripheral and coronary circulation leads to the increased levels of cyclic guanosine monophosphate in vascular smooth muscle cells under phosphodiesterase-3 inhibitor treatment.⁷

Elimination route: 85% of drug is cleared through renal secretion with 15% undergoing glucuronidation and is 70% is protein bound.

Intravenous Dosing: Loading doses: 25 to 50 mcg/kg given over 10 minutes.

Infusion rates: ranging between 0.375 and 0.75 mcg/kg/min

Side effects: headaches, syncope, severe hypotension, ventricular tachyarrhythmia, cardiac ischemia, bronchospasm, hypokalaemia, thrombocytopenia, Torsades de pointes, sudden cardiac death.⁸

Material & methods:-

Our study was done in DVVPP's Medical College & Hospital, Ahmednagar-414111 (MS). It was Randomized, double-blind used on 2 parallel treatment groups of pediatric patients undergoing cardiac surgery. The study was done only after approval by its institutional review board. Before enrollment, written informed consent was obtained from each patient's parent or guardian.

Study design: prospective randomised study

Time period: June 2019 to June 2020

Inclusion criteria: children up to 1 year undergoing congenital corrective cardiac surgery.

Exclusion criteria: preterm neonates (<36 weeks of gestation), preexisting low cardiac output syndrome, body weight less than 3kg, pre-existing renal failure (creatinine value more than or equal to 1.5mg/dl 48 hours before surgery), pre-existing thrombocytopenia and preoperative use of milrinone. The physicians were given the option to discontinue study drug between 24 and 36 hours for patients who appeared clinically well.

Sample size: 30 children up to 1 year undergoing congenital corrective cardiac surgery were selected according to inclusion, exclusion criteria.

Methodology: Children were randomly divided into two groups in 1:1 ratio within 90 minutes after arriving in ICU, to receive either loading dose of milrinone (50mcg/kg/min over 10 min) or to receive low dose milrinone infusion (0.5mcg/kg/min and continued postoperatively).

Before induction of anaesthesia non-invasive monitors were used. Variety of drugs such as ketamine, thiopentone, pancuronium, fentanyl, morphine and sevoflurane, often in combination as needed were used along with anaesthetic techniques. After induction and intubation of patients, for invasive monitoring such as arterial line and CVP line were inserted and connected to the transducers. Priming of CPB circuit was done with a 250 mL of a combination of plasmalyte, 20% albumin or fresh frozen plasma, Ringer lactate, bicarbonate, heparin, mannitol, steroids and whole blood to achieve a hematocrit between 28-30% in children. Hypothermia to 22°C– 28°C and circulatory arrest were used in some patients. For all patients, modified ultrafiltration (MUF) was used during cardiopulmonary bypass.

Group A: Milrinone infusion was started without loading dose at 0.5mcg/kg/min at the beginning of CPB and continued postoperatively (0.5-0.75 mcg/kg/min) in the paediatric cardiac surgical ICU.

Group B: Milrinone was started as a loading dose of 50mcg/kg over 10 min after aortic declamping and continued as infusion postoperatively at 0.5-0.75 mcg/kg/min in the pediatric cardiac surgical ICU.

Patients monitoring:

Monitoring of patients in the form of hemodynamic parameters such as heart rate, mean arterial blood pressure (MAP), central venous pressure (CVP). From arterial blood gases (to check the PH, vSpo2 and lactate levels) were done through samples withdrawal from arterial line.

Laboratory monitoring of urine output, urea, creatinine and liver enzymes levels were done. The readings were collected before the beginning of study medication i.e. base line, at 1st, 6th, 12th postoperative hours in the ICU.

Lactic acidosis, low mixed venous oxygen saturation and low urine output used for assessing low cardiac output. Postoperatively for unstable patients echocardiography was done to assess contractility, valvular functions and to exclude pericardial effusion affecting the hemodynamics of patients.

Limitation of study: Option to doctors were gives to discontinue study drug between 12 and 24 hours for patients who appeared clinically well . We could not measure the cardiac index as the proper sizes of Swan Ganz catheter for children were not available in cardiac center.

Statistical methods: Data were statistically described in terms of mean ± standard deviation . Paired t test used for comparison.A probability value less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2010 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science, India) version 15 for Microsoft Windows.

Results:

1. Sex:

Our study involved 30 patients classified into two groups:

Group A, involved 15 patients (8 female and 7 male) and Group B, involved 15 patients (7 female and 8 male). No significant difference regarding the sex of patients in both groups (p value>0.05).(Table 1)

2. Surgical data of patient:

The cardio-pulmonary bypass time in group A 203 min and group B 222min and aortic crossclamping time in group A 1 20 min and in group B 115min between the patients of both groups was insignificant as p value > 0.05. (Table 1)

Table 1:- Sex and surgical data of patient in mean +/- SD

Data	Group A	Group B	p-value
Age in months	8.4(2.06)	7.8(2.52)	>0.05
Weight in kg	7.4(2.6)	7.38(2.4)	>0.05
Sex F/M	8/7	7/8	>0.05
CPB (min)	160(22.1)	170(20.2)	>0.05
Aortic cross clamping (min)	100(21.0)	110(20.0)	>0.05

3. Hemodynamic data of patients:

The study showed that the weaning from cardiopulmonary bypass was easier in patients of group A than group B. Inotropic support, mechanical supports such as extracorporeal membrane oxygenator (ECMO), and pacing during weaning from CPB and postoperatively in the pediatric cardiac surgical intensive care unit are less in patients of group A than group B.Heart rate,central venous pressure comparison of both groups was insignificant (P>0.05) but regarding the mean arterial blood pressure,at the 1st and 6th hour of assessment (P<0.05) the comparison was significant but insignificant at 12th hour (P>0.05). In patients of group B mean arterial pressure was dropping, for few minutes and was managed with dopamine infusion. (Table 2).

Table 2. Hemodynamic data of patients represented in mean +/- SD

Item	Timing	Gr oup A	Gr oup B	P value
Heart rate (min)	(Base)	148.9(10.40)	143.5(11.5)	>0.05
	1 st hour	144.6(16.4)	146.4(23.4)	>0.05
	6 th hour	142.26(4.57)	143.5(7.8)	>0.05
	12 th hour	142.6(4.9)	144.5(4.5)	>0.05
Mean arterial pressure (mm of Hg)	(Base)	66.4(8.51)	57.40(6.90)	>0.05
	1 st hour	67.3(5.9)	54.4(8.9)	<0.05
	6 th hour	65.5(5.9)	58.1(6.7)	<0.05
	12 th hour	56.7(6.3)	54.55(5.2)	>0.05
CVP (mm of Hg)	(Base)	14.40(1.72)	14.53(1.30)	>0.05
	1 st hour	14.2(1.8)	14.31(1.8)	>0.05
	6 th hour	14.5(3.6)	14.7(4.0)	>0.05
	12 th hour	12.5(2.9)	15.6(5.2)	<0.05

4. Laboratory data of patients:

Rise in lactate level signifies metabolic acidosis as seen more in patients of group B than that of group A. The lactate level was within normal level before starting the milrinone in both groups with insignificant difference (P value>0.05) but at other timepoints the lactate level was higher in patients of group B than group A with significant difference (P<0.05). The urine output was insignificant before starting milrinone (P>0.05) after starting milrinone, increased significantly more in patients of group A in relation to patients of group B at

other time points ($P < 0.05$). Central venous oxygen saturation comparison was insignificant at the baseline ($P > 0.05$) and lower in patients of group B than that of group A with significant difference at 12th hour ($P < 0.05$). The urine output was insignificant before starting milrinone ($P > 0.05$), but increased significantly after starting milrinone as seen in patients of group A compared to group B at other timepoints ($p < 0.05$) (Table 3)

Table 3:- Laboratory data of patients represented as mean +/- SD

Data		Group A	Group B	P value
Central venous oxygen saturation (vSpO ₂)	(Base)	51.21(10.19)	49.27(6.06)	0.574
	1 st hour	54.6(6.6)	54.7(5.8)	>0.05
	6 th hour	52.6(5.8)	51.7(6.2)	>0.05
	12 th hour	52.3(5.7)	55.8(5.2)	<0.05
Urine output (ml/kg/hr)	Base	3.38(0.79)	3.55(0.87)	0.610
	1 st hour	3.48(1.20)	3.24(1.8)	>0.05
	6 th hour	3.65(0.65)	3.44(0.69)	<0.05
	12 th hour	3.65(0.65)	2.44(0.69)	<0.05
Serum lactate (mg/dl)	Base	1.6(0.3)	1.7(0.4)	0.215
	1 st hour	2.9(1.6)	2.57(1.9)	>0.05
	6 th hour	4.5(1.2)	3.9(1.7)	>0.05
	12 th hour	3.7(0.65)	4.2(0.69)	<0.05

5. Postoperative outcome of patients:

For all patients, dopamine was added to milrinone during weaning from CPB but, adrenaline was added in 6 patients of patients of group A and added to 12 patients of group B, noradrenaline was only needed for 3 patients of group B postoperatively in the ICU and the P-value of total inotropic support was significant (P value < 0.05). Pacing was needed for 3 patients of group A and 4 patients of group B. The ECMO was used only in 2 patients of group B and the P-value of total mechanical support was insignificant (P value > 0.05). Also, the urea and creatinine were elevated in 3 patients of group A and 5 patients of patients of group B. Liver enzymes levels became elevated more than 2 folds on the second postoperative day in some patients of both groups but the difference was insignificant. There were no complications related to milrinone in patients of both

groups (Table 4).

Table 4:- Postoperative outcome of patients represented as n which is no. of patients

	Group A (mean +/-SD)	Group B (mean +/-SD)	P value
Inotropic support	6(6 +/-1.6)	159(15 +/-1.9)	<0.05
Pace maker	3(4.6 +/-1.9)	4(3.9 +/-1.1)	>0.05
ECMO	-	2(1 +/-3.6)	>0.05
Deranged Renal function test	3(1.6 +/-2.4)	5(1.7 +/-3.1)	>0.05
Elevated Liver enzymes	2 fold rise (70 +/- 23.1)	2 fold rise (80 +/- 19.8)	>0.05

Discussion

For tissue perfusion, adequate cardiac output, oxygenation and normal organs functions are important factors. Several studies have showed that, the low cardiac output syndrome is common after congenital cardiac surgery and leads to increased requirement for inotropes, mainly catecholamines to improve cardiac performance after cardiac surgery. This will increase heart rate and myocardial oxygen consumption, down-regulation of beta-adrenergic receptors, increases the myocardium work, increase in systemic vascular resistance, impair tissue perfusion and development of metabolic acidosis. The acidosis depresses the myocardium, and impairs the sensitivity and response to catecholamines and vicious circle will be developed. The prevention or decreasing the incidence of low cardiac output syndrome will decrease postoperative morbidity and mortality.

In our study, we found that the loading dose of milrinone in patients of group B was associated with mean arterial pressure dropping but it was not severe and for few minutes and managed only with dopamine infusion. The study showed that the weaning from Cardiopulmonary bypass in patient of group A was easier than patients of group B. Also, the requirement for ionotropes for hemodynamic support to maintain the mean arterial blood pressure from 50 to 60 mmHg was higher and significant in patients of group B than in group A.

The mechanical support such as pacing and ECMO to the myocardium was needed only in patients of group B because of failure to wean the patients from cardiopulmonary bypass, but statistically was insignificant. The central venous oxygen saturation was lower in patients of group B than group A, and also the lactic acidosis was more in group B than group A. Inadequate tissue perfusion occurred as a result of low cardiac output or vasoconstricting effect of catecholamines and the result was impaired oxygen delivery, more oxygen requirement by the tissues lead to anaerobic glycolysis and development of lactic acidosis. For patients with decreased urine output in both groups, fluids, furosemide and mannitol doses were given but no response. Furosemide infusion was started but not improving well. Finally peritoneal dialysis was used until the complete recovery of kidneys by 7-15 days. The good results with early uses of milrinone at the beginning of Cardiopulmonary bypass may be due to high level of milrinone in the blood and its effect on the tissue perfusion during and after cardiopulmonary bypass.

The same results were seen in study done by Rabie soleman and Hasan in 2012 included 40 paediatric patients undergoing cardiac surgery in year 2012, showed that patients who were given loading dose of milrinone, it was easier for weaning of CPB and mean arterial pressure was also maintained in them, heart rate, central venous pressure remain unchanged like our result. Inotropes were required in children who have been on low dose of milrinone infusion.⁹

The study done by Timothy M. Hoffman, MD; Gil Wernovsky in year 2003 on 238 children 6 years of age or younger without preoperative LCOS who were undergoing biventricular repair of certain cardiac lesions involving cardiopulmonary bypass showed that clinical features in the 44 patients with LCOS 54.5% with oliguria, 31.8% with tachycardia, and 2.3% with a cardiac arrest; 45.5% had a widened (30%) arterial-mixed venous oxygen difference, and 22.7% metabolic acidosis. The management of LCOS included the initiation of a new inotropic agent in 84.1%, escalation of existing pharmacological support in 43.2%, and initiation of extracorporeal membrane oxygenation in

4.5%. These were the findings seen in the group who were given low dose infusion of milrinone infusion. Findings are consistent with my result.¹⁰

This explanation may be supported by study done by Athena F. and his colleges. For neonates undergoing stage I reconstruction of hypoplastic left heart syndrome an initial loading dose of 100 mcg/kg on CPB resulted in plasma concentrations similar to those observed in other therapeutic settings, the effect of modified ultrafiltration is to increase plasma milrinone concentrations by approximately 35%. Assuming that renal clearance is minimal during this time, it is possible that modified ultra-filtration provides both hemoconcentration and a second bolus effect, because blood that was returned to the patients from the venous system had milrinone.¹¹

Conclusion:-

Early use of milrinone in children upto 1 year undergoing cardiac surgery lead to easy weaning from cardiopulmonary bypass, decreased the requirement for pharmacological and mechanical support and decreased the incidence of low cardiac output syndrome and no complications after pediatric cardiac surgery related to milrinone in our study patients.

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