VOLUME-8, ISSUE-12, DECEMBER-2019 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Anaesthesiology

A COMPARISON OF HEMODYNAMIC EFFECTS OF MILRINONE AND LEVOSIMENDAN IN PATIENTS UNDERGOING CARDIAC SURGERY WITH PULMONARY HYPERTENSION.

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KEYWORDS :

INTRODUCTION

Pulmonary artery hypertension(PAH) is a major risk factor for increased mortality and morbidity in patients undergoing cardiac surgery(1,2). Prognosis depends on presence or absence of postoperative residual PAH(3) by lowering postoperative Pulmonary artery pressure(PAP) would give better results. Milrinone, a phosphodiesterase III inhibitor, is commonly used during the post cardiopulmonary bypass (CPB) period in combination with epinephrine or norepinephrine to decrease PAP and to provide a synergistic positive inotropic effect in the presence of CPB-induced downregulation of a -adrenoreceptor(4,5). Levosimendan enhances myocardial contractility by sensitizing troponin C to calcium within cardiomyocytes(6). Unlike other inotropes, it reduces the development of arrhythmias and the incidence of cardiotoxicity because an increase in intracellular calcium does not occur(7). Levosimendan also has a vasodilating effect on systemic,coronary,and pulmonary vasculature through activation of adenosinetriphosphate-sensitive potasium channels and phosphodiesterase inhibition(8,9). It has been used to decrease pulmonary vascular resistance, and restore better right ventricular- pulmonary artery coupling after pulmonary embolism,(10) in decompensated heart failure,(11) and after mitral valves surgery(12) because of its beneficial effects of improving biventricular systolic and diastolic function and better biventricular function comparable with Milrinone when used in combination with epinephrine during the post bypass period.

MATERIALS AND METHODS

This prospective randomized study was conducted a tertiary care hospital between December 2017 and September 2018. After written informed consent, 40 adult patients of either sex undergoing mitral or aortic valve replacement with PAH (Mean PAP 40 mmHg, or systolic PAP exceeding 50% of systemic systolic pressure) were enrolled in the study. Patients with severe renal and hepatic dysfunction, age more than 65 years and less than 20 years, EF less than 50 % for regurgitant lesion, less than 40% for stenotic lesion, emergency surgery,or those requiring preoperative inotropes were excluded from the study. Anesthesia was induced using Fentanyl, 3 to 5 mic g/kg, and Propofol (0.3-0.5mg/kg). Rocuronium, 1mg/kg, was used for neuromuscular relaxation. For maintenance of anesthesia, all patients received Sevoflurane and an intravenous maintenance dose of Fentanyl (1 mic g/kg) per hour and Rocuronium 0.2 mg per 30 min. Before CPB, activated clotting time of more than 480 seconds was achieved using intravenous heparin(400 IU/kg). Cardioplegia (delnido) was used. Moderate hypothermia (28-32 degree C) was estabilished in all patients. CPB pump flow was maintained between 2 to 2.5 L/min/m2, with a mean arterial blood pressure target of 50 to 80 mmHg. All patients were rewarmed to 36 degree C nasopharyngeal temperature before separation from CPB. At the start of rewarming, patients were randomly assigned into either group 1 (Milrinone) or group 2 (Levosimendan) using sealed envelope method. Group 1 patients received Milrinone, infusion at a rate of 0.5 mic g/kg/min ; Group 2 patients received Levosimendan infusion at a rate of 0.1 mic g/kg/min. Separation from CPB was achieved using epinephrine 0.05 mic g/kg/ min in both groups, and norepinephrine was started if mean arterial blood pressurere maintained less than 60mm Hg and systemic vascular resistance index (SVRI) was less than 1800 dynes sec /cm5/m2. No additional agents were used for pulmonary vasodilatation. Patients were transferred to the cardiac surgical intensive care unit (ICU) for elective mechanical ventilation to maintain oxygenation and normocapnia. Both Milrinone and Levosimendan infusions were continued for 24 hours in the postoperative period. Heart rate, invasive blood pressure, mean PAP, and central venous pressures were monitored continuously for 24hours in the ICU after surgery. Cardiac index , SVRI was measured using flow trac . ejection fraction(EF) and indirect PAP were measured by echo before surgery, after induction, after weaning from bypass , before transfer to the ICU, 1 hour, 6 hours, 12 hours and 24 hours post-ICU arrival.

STATISTICAL ANALYSIS

The determined sample size was 20 patients in Group 1 (Milrinone) and Group 2 (Levosimendan). Numerical result was presented as mean+/- SD. Mean was compared by the student 't' test. Categorical data were compared using chi square test. A p value < 0.05 was considered significant. All statiscal analysis done by using android mobile application " p value- a statistical tool".

RESULTS

40 patients fulfilled inclusion criteria and completed the study. This study was prospective, randomised and double blind type. The demographic profile, preoperative clinical characteristics, and intraoperative variables were comparable between the two groups . both groups were comparable. levosimendan group was showing significantly increase in heart rate post bypass than milrinone. MAP , mean PAP and SVRI was more decreased with levosimendan. Post bypass to 1st hr of ICU , this was significant. Cardiac index was more increased with levosimendan but overall this was nonsignificant. EF was more increased with milrinone but was nonsignificant. 3 patients were needed noradr infusion (>0.05 mic g/kg/min) on 1st hr of ICU stay for milrinone group other than adrenalin infusion 0.05 mic g/kg/min. For levosimendan group 6 patients were needed noradr infusion (>0.05 mic g/kg/min) on 1st hr of ICU, 3 pt were still needed noradr infusion (>0.05 mic g/kg/min) on 24 hrs of ICU stay other than 0.05 mic g /kg/min of adr infusion.

Table 1: Patient characteristics and clinical parameters in 2 groups

S.NO		Mean +/- SD		P value
		Group 1	Group 2	

1.	AGE (years)	45.21+/-11.12	39.65+/-12.34	0.14
2.	BODY SURFACE AREA(m2)	1.51+/-0.12	1.54+/-0.15	0.48
3.	WEIGHT(kg)	53.5+/-12.8	55.1+/-11.8	0.68
4.	HEIGHT(cm)	164.7+/-6.7	166.8+/-7.8	0.36
5.	DURATION OF SYMPTOM(years)	6.6+/-3.8	5.6+/-3.5	0.39
6.	DURATION OF MEDICAL TREATMENT(years)	4.1+/-2.8	3.8+/-2.6	0.72
7.	SEVERE MITRAL VALVE STENOSIS	4	4	
8.	SEVERE MITRAL VALVE REGURGITATION	5	5	
9.	SEVERE AORTIC VALVE STENOSIS	6	5	
10.	SEVERE AORTIC VALVE REGURGITATION	5	6	
11.	MEDIAN MITRAL VALVE SIZE(mm)	27	28	
12.	MEDIAN AORTIC VALVE SIZE(mm)	21	20	
13.	TRICUSPID VALVE REPAIR(no.)	5	4	
14.	TRICUSPID VALVE RING ANNULOPLASTY	4	3	
15.	AORTIC CROSS CLAMP TIME(min)	110+/-50.1	108+/-48.8	0.88
16.	CPB (min)	176+/-65	172+/-59.7	o.84
17.	MINIMUM TEMPERATURE	29.8+/-1.4	29.6+/- 1.3	0.64

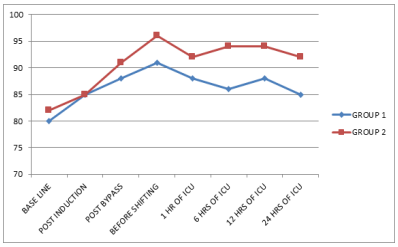

Fig 1: heart rate

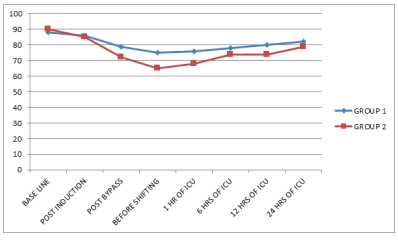

Fig 2: MAP

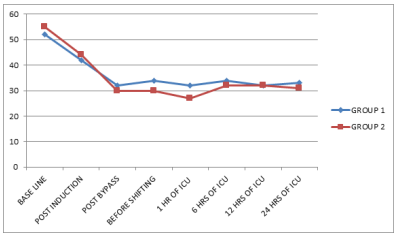

Fig 3: mean PAP

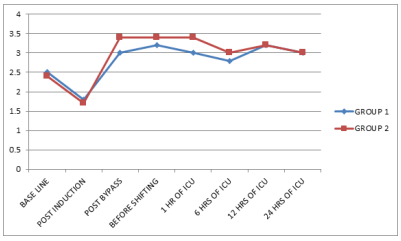

Fig 4: cardiac index

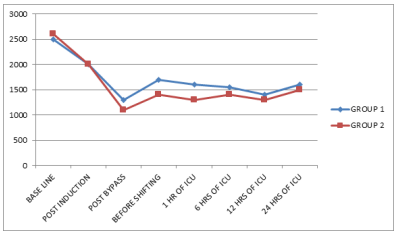

Fig 5: SVRI

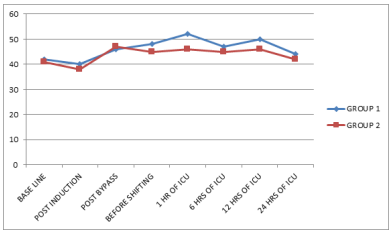

Fig 6: EF(stenosis)

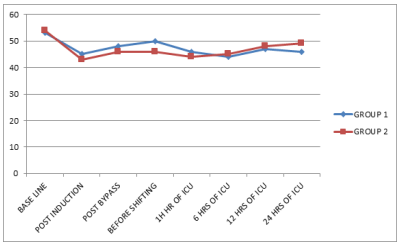

Fig 7: EF(regurgitation)

DISCUSSION-

Heart disease patients with valvular pathology having PAH demonstrate decreases in PAP after surgical correction due to release of left-sided obstruction(13).This was reflected in the study but persistence of at least a moderate level of pulmonary hypertension in both groups also was documented. The reason of residual pulmonary hypertension was due either morphologic changes in pulmonary vasculature and/or increased pulmonary vasculature reactivity by various events during cardiac surgery.

The results of this study showed that both Milrinone and Levosimendan caused nearly similar decrease in mean PAP and maintained comparable systolic function. Kleber et al(14) demonstrated that levosimendan caused a 14% reduction in mean PAP and a 12% reduction in PVRI from baseline in a nonsurgical setting. Wang et al(15) showed that Milrinone caused significant reduction in PAP in patients undergoing mitral valve surgery. Price et al(16) suggested that both Levosimendan and Milrinone were useful in PAH associated with pulmonary vascular and right ventricular dysfunction.

Both Levosimendan and Milrinone after cardiac surgery have been associated with improved cardiac index. Shawaf et al(17) found Levosimendan to be superior to Milrinone in increasing cardiac output in diabetic patients with low ejection fraction undergoing elective coronary artery surgery. Lechner et al(18) showed a similar increase in cardiac index with either Levosimendan or Milrinone during neonatal and infant cardiac surgery.

Levosimendan infusion has been associated with tachycardia(19). A higher degree of vasodilatation and increased requirement of Norepinephrine also have been associated with the use of Levosimendan(20). This study's results also showed higher heart rate and increased requirement of Norepinephrine in the Levosimendan group.

CONCLUSIONS:

The results of this study concluded that Levosimendan was not hemodynamicaly better than Milrinone for PAH patients. Levosimendan therapy result greater increase in heart rate, decrease in systemic vascular resistance and greater need for Norepinephrine than in patients who received Milrinone.

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