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Outcome of Prophylactic Use of Levosimendan and Milrinone in Open Heart Surgery With Compromised Ventricular Function–A Comparative Study.

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ABSTRACT

Background: Compromised ventricular function complicates the postoperative course after open heart surgery. Incidence of low-output syndrome (LOS) after cardiopulmonary bypass(CPB) is 30%. Vaso active therapy is required for weaning from bypass. Levosimendan is one of the new class of inodilator useful in refractory cardiac failure. Objective: The aim of this randomized control trial is to detect whether prophylactic levosimendan infusion is superior to milrinone in preserving better tissue perfusion, in decreasing complications related to low output syndromes and better hemodynamic control and to evaluate the efficacy of intravenous levosimendan infusion in decreasing the use of high dose of conventional inotropes and consequent prolonged hospitalization in open heart surgery patients with preoperative compromised ventricular function. **Methods:** Thirty consecutive patients with compromised cardiac function belongs to American Society of Anesthesiologists(ASA) physical status III who underwent open-heart surgery with CBP were randomly divided into two groups. Gr-L received levosimendan (loading dose of 12 µg/kg over 10 mins followed by infusion dose of (0.1 µg/kg /min) and Gr-M received milrinone loading dose of 50 µg/kg over 10 mins followed by infusion dose of (0.5 µg/kg/ min)after anesthesia induction. Hemodynamic profile, mixed or central venous oxygen saturation (SVO2, SCVO2) which are surrogate markers for cardiac output, tissue perfusion were recorded, and blood obtained for troponin level. **Results:** SVO2 and SCVO2 were significantly higher in Gr L versus Gr M. Postoperative troponin- I concentrations, need of other inotropes incidence of arrhythmia, re-intubation, Intensive care unit(ICU) stay and hospital stay were significantly decreased in Gr L. **Conclusion:** Prophylactic levosimendan infusion maintains better hemodynamic control, tissue perfusion, myocardial protection and lesser complications in patients with compromised ventricular function.

Keywords: milrinone, levosimendan, mixed and central venous oxygen saturation, hemodynamic response.

INTRODUCTION

The calcium sensitizer levosimendan was developed as a treatment for acutely decompensated severe chronic heart failure. Now it is also used in different scenarios like in patient at risk of low cardiac output syndrome or perioperative heart failure. The incidence of a low-output syndrome (LOS) after cardiac surgery with cardiopulmonary bypass (CPB) in patients with depressed ventricular function is approximately 30 %.[1] LOS was defined as cardiac index (CI) ≤2.2 L/min/m^2, pulmonary capillary wedge pressure (PCWP) ≥18 mmHg, mean arterial pressure (MAP) ≤50 mmHg, and systemic vascular resistance (SVR) ≥1,500 dynes/sec/cm^{-5}.

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LOS causes delayed recovery, organ failure, ICU stays, increased hospital costs and adds to the risk of early postoperative mortality.[2,3] So it requires more monitoring, more medication. To prevent or lessen these adverse outcomes, a postsurgical low-output state should be prevented whenever possible. The traditional inotropes, such as epinephrine, dobutamine and milrinone (phosphodiesterase inhibitor) improves contractility but there is increased myocardial oxygen demand with consequent risk for ischaemia, arrhythmia, hypotension[4], Levosimendan is a promising newer alternative inotropic agent with possible clinical indication after open-heart surgery.[5-9] It is being used successfully in post CPB low output syndrome. Incidence of hypercalcemia and arrhythmia are also less with it. It has a long acting metabolite with a half-life of 80 h.[10-13] Levosimendan improves the function of stunned myocardium in patients with acute myocardial infarction undergoing angioplasty.[14]

MATERIALS AND METHODS

After getting the institutional ethical committee's approval this prospective, randomized trial was conducted at SCBMCH, Cuttack, Odisha. All patients gave written informed consent. The study population consists of 30 consecutive patients of any age of either sex with compromised cardiac function [New York Heart Association (NYHA) III IV preoperatively, left ventricular ejection fraction (LVEF) < 45% by echo study] ASA III who underwent open-heart surgery with CBP (elective CABG surgery or valve surgery). Exclusion criterias includes symptomatic congestive heart failure (CHF) while the patient was on bed rest, preoperative LOS, pre-existing renal failure, liver and neurological disorder, preoperative cardiopulmonary resuscitation, preoperative use of milrinone or levosimendan or allergy to these drugs. Pre-anaesthetic evaluation was performed .All patients were pre-medicated with tab alprazolam 0.1 mg / kg orally and tab ranitidine 150 mg on the night before surgery and morphine sulphate 0.1 mg / kg IM one hour before surgery. After arrival of patient in ot standard anaesthesia monitors (ecg leads with ST segment and arrhythmia monitoring capability, pulse oximeter probe, NIBP) were attached. Radial artery canulation done under local anesthesia. After induction of anesthesia, a continuous cardiac output pulmonary artery catheter, a central venous catheter. A urinary bladder catheter with a temperature probe was inserted for temperature and urine-output monitoring.

Anaesthetic technique: A standard anaesthetic technique for all patients was performed. All patients were induced with midazolam (0.05 mg/kg), fentanyl (2 µg/kg), propofol (1.0 mg/ kg), and rocuronium (0.9 mg/kg) through intravenous route. Anesthesia was maintained with isoflurane (0.5-1.0%) with N_2O and O_2 in 50:50 ratio and supplemental propofol 50- 100 ug/kg/min throughout the surgery and fentanyl 1-2 ug /kg i.v. as required. All operations were performed through a median sternotomy using a standard surgical technique. After anesthesia induction the patients were randomized by sealed envelopes to receive levosimendan (levosimendan group Gr L) or milrinone (milrinone group Gr M) as continuous infusion. Levosimendan loading dose of 12 µg/kg over 10 mins followed by infused at a rate of 0.1 µg/ kg min and milrinone loading dose of 50 µg/kg over 10 mins followed by infused at a rate of 0.5 µg/kg/min. The 2 groups received dobutamine 5ug/kg/min started after aortic cross clamp release. Simultaneous infusion of nor-epinephrine was added, when required to maintain mean arterial pressure (MAP) > 65 mmHg. Before aortic canulation, the patients were anti coagulated with heparin 4 mg/kg to reach ACT > 400. The CPB was conducted with a flat sheet membrane oxygenator using non-pulsatile flow. The circuit prime consisted of ringer's solution 1800 ml, 25% mannitol 100 ml and heparin 5000 IU. The pump flow was maintained at 2.0-2.5 litre/min/m^2. Cold cardioplegic solution was given after aortic cross- clamping for myocardial protection. After weaning from CPB, anesthesia maintained with oxygen and isoflurane. Protamine sulphate was infused slowly over 20 min to neutralize heparin effect and achieve ACT within 20% of baseline. After skin closure, all patients were transferred to ICU, intubated and mechanically ventilated. In the ICU, the patient's condition was evaluated and further sedation was maintained by propofol (infusion 2-3 mg/kg/h) and intermittent boluses of morphine (2-4 mg every 30 minutes as needed).

Hemodynamic measurements: Hemodynamic profile like Heart rate, arrhythmias, mean arterial pressure, mixed and central venous oxygen saturation(SVO2,SCVO2) were obtained after the induction of anesthesia and before starting the assigned pharmacologic treatment (base), after sternotomy, after separation from CBP, and in ICU on arrival (T0), 6 (T6), 12 (T12), 24 (T24) hours later. During and after surgery, nor-epinephrine infusions were administered to maintain MAP ≥65 mmHg. The nor-epinephrine infusion was started for hypotension with SVR ≤600 dynes/sec/cm-5. Pulmonary capillary wedge pressure was kept in all patents between 12 and 18 with fluid administration. Blood samples were collected from pulmonary artery catheter and central venous catheter after induction, sternotomy, post bypass time and after completion of surgery in ICU. Weaning from inotropic support was based on hemodynamic profile and patient physical status in ICU. Criteria for extubation in ICU were a) patient responsive to verbal command b) oxygen saturation >94% on inspired 02 concentration <50% c) respiratory rate <20/min and no obvious respiratory distress d) Pa CO2 <50 mmhg e) Ph>7.3 f) tidal volume 7ml/kg on pressure support<12 cm H_2O above end expiratory pressure g) chest tube drainage <100ml h) hemodynamic stability (not requiring significant inotropic support and no uncontrolled arrhythmia). Post op complication were noted during ICU stay and treated accordingly. Criteria for discharge from ICU were alert, cooperative patient, having adequate spontaneous ventilation, no inotropic support, no arrhythmia, urine output >0.5 ml/kg/hr

Statically Analysis –
The data were collected and analyzed by paired sample 't' test and expressed as mean ± standard deviation. The statistical difference was done by 2-tailed test. P value was significant if < 0.05 these statistics were done by using SPSS 10 software.

RESULTS

Preoperative and surgical patient characteristics are summarized in [Table 1]. There were no differences among groups in the pre- or intraoperative data except that 94% of patients in the levosimendan group and only 61% in the milrinone group could be weaned from CPB at first attempt ($p < 0.05$). Hemodynamic data are listed in [Table 2]. HR, MAP, CVP PCWP were not different among groups as adherence to the protocol for maintaining these variables within specified ranges SVO2 [Figure 1]. SCVO2, which are the surrogate marker of Cardiac output and tissue perfusion after surgery was initially higher than at baseline in both, groups but was significantly higher in levosimendan group versus milrinone group [Figure 2]. This difference was observed throughout the remainder of the observation period. Troponin level listed in [Table 3]. Levosimendan-treated patients had lower postoperative troponin- I concentrations than milrinone group starting from post-CBP but statistically significant differences were observed postoperatively at T24 ($P<0.05$) [Figure 3]. Inotropic and vasoactive medication and postoperative outcome data are listed in [Table 4]. The total dose and duration of administration of dobutamine and nor-epinephrine were significantly higher in milrinone group than Levosimendan group [Table 4; Figure 4]. Re-intubation occurred in five patients of milrinone group but in levosimendan group none required re-intubation. The ICU stay and the duration of hospitalization were significantly decreased in levosimendan group, compared to milrinone group. The incidence of postoperative atrial fibrillation was significantly lower in levosimendan group.

Table 1: Baseline Demographic Characteristics.

	Levosimendan gr 1 n-15	Milrinone gr 2 n-15
Age(years)	56±12	58±11
sex	13/2	12/3
Weight(kg)	57.3±5.6	55.6±4.8
Height (cm)	158±4.1	161±4.5
EF%	31±4	30±5
CPB(time in min)	122±31	128±32
Aortic cross clamp time(min)	82±42	79±34
>1 attempt to wean from CPB(%)	1(6.6%)*	6(39.6%) p<0.01

Data are mean ± SD unless stated otherwise. *p< 0.05 Abbreviations: EF, left-ventricular ejection fraction %; CPB, cardiopulmonary bypass time.

Table 2: Peri- and Postoperative Hemodynamic Changes over Time.

	Base	After sternotomy	*Post-CPB*	*ICU T0*	*ICU T6*	*ICU T12*	*ICUT24*
HR (beats/min)							
Levosimendan	65.81 ±8.53	68.68 ±9.12	94 ± 9*	96 ± 11*	92 ± 9*	94 ± 6*	92 ± 7*
Milrinone	67.97 ±8.99	68.77 ±9.22	91 ± 7*	92 ± 7*	91 ± 8*	92 ± 7*	89 ± 9*
MAP (mmHg)							
Levosimendan	71 ± 8	75 ±6.7	73± 7	71 ± 7	76 ± 13	76 ± 12	76 ± 10
Milrinone	73 ± 7	74.6 ±6	72 ± 9	70 ± 9	74 ± 9	77 ± 10	77 ± 12
PCWP (mmHg)							
Levosimendan	15 ± 2	16 ±2	16 ± 3	17 ± 1	16 ± 2	16 ± 3	15 ± 2
Milrinone	16 ± 3	15 ±3	17 ± 2	16 ± 2	15 ± 3	16 ± 2	16 ± 2
CVP (mmHg)							
Livosimendan	11 ± 3	13 ±1	12 ± 3	14 ± 3	14 ± 3	13 ± 4	13 ± 3
Milrinone	12 ± 2	14 ±1	14 ± 2	15 ± 3	14 ± 4	12 ± 4	14 ± 2
SVO_2							
Levosimendan	63.59 ±4.49	66.06 ±4.88	78.22±4.2*!	70.11±5.27*!	74.83±3.98*!	68.74±4.72*!	73.8±4.43*!
Milrinone	64.65 ±4.01	64.29±3.51	65.29±4.64*!	64.58±3.09*!	68.35±2.87*!	65.73±2.59*!	67.8±2.27*!
$ScVO_2$							
Levosimendan	61.39 ±3.65	64.35±3.94	75.24±4.53*!	71.94±4.69*!	77.28±3.64*!	67.72±3.81*!	68.6±3.9*!
Milrinone	61.03±3.1	62.87±3.07	66.35±4.8*	67.42±3.6*!	68.9±2.4*!	65.77±2.37*!	64.7±2.2*!

Data are mean ± SD. HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; SVO2,SCVO2-mixed and central venous oxygen saturation

*Statistically significant difference compared with base ($p < 0.05$).

†Statistically significant difference compared with milrinone group ($p < 0.05$)

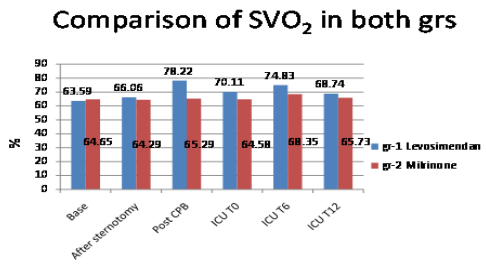

Figure 1: Comparison of SvO2

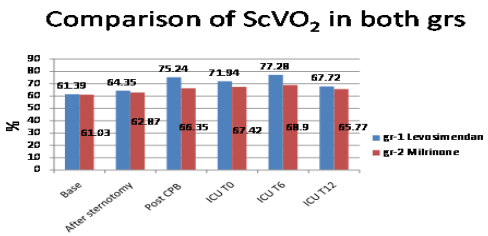

Figure 2: Comparison of ScVO2

Table 3: Biochemical Data.

	Preoperative	T0	T6	T12	T24
TROPONIN1					
Levosimendan	0.13±0.28	0.8±0.22*	1.8±0.09*	2±1.25*	2.1±0.43*
Milrinone	0.14±0.27	2.1±0.85*	3.71±1.63*	4.65±2.27*	4.83±3.02*†

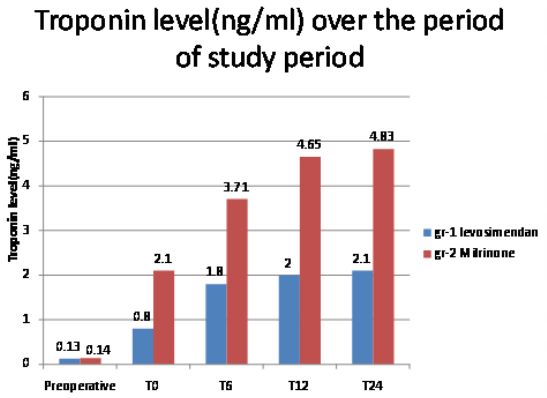

Figure 3: Troponin level.

Table 4: Inotropic and Vasoactive Medication and Postoperative Outcome Events.

	Levosimendan (n = 15)	Milrinone (n =15)
Dobutamine		
Total dose(ug/kg)	4,053 ±1,957 *	15,158±2,267
Time (h)	11±4*	34 ± 10
Norepinephrine		
Total dose (ug)	4,986 ± 3502 *	21,451 ± 8,142
Re-intubation	0 *	5
LOS ICU (h)	53±9*	121 ±67
LOS hospital (d)	11±4*	21 ± 7
Arrythmia	1*	7

Data are mean ±SD
Abbreviation: LOS, length of stay.
*Statistically significant difference compared with milrinone group (p<0.05)

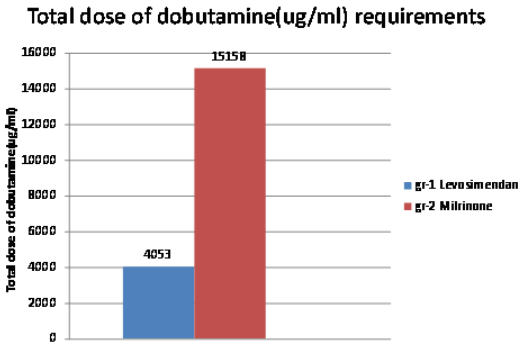

Figure 4: Total dose of Dobutamine.

DISCUSSION

Postoperative myocardial stunning is a common phenomenon after cardiac surgery, even with the use of contemporary cardio-protective methods. So transient myocardial dysfunction easily sets in which is more pronounced in patients with impaired left ventricular function before surgery. Thereby postoperative inotropic support is needed.[15,16] In this study, levosimendan and milrinone commonly known as inodilator were used. Milrinone is an inodilator which acts by inhibiting PDE III enzymes and acts independently of beta receptors. It lessens myocardial ischaemia and cell damage. Levosimendan opens the K ATP channels and inhibits PDE III without increasing cAMP. Levosimendan increases myocardial contractility, vascular smooth muscle relaxation, coronary blood flow and cardiac output by sensitizing myofibril to calcium .It causes vasodilatation by opening up opening of potassium channels without increasing oxygen consumption of the heart muscle cells. In our study we used two parameters like mixed venous oxygen saturation and central venous oxygen saturation (SVO2 and SCVO2) which measures the end result of 02 consumption and delivery to tissue. It can be used as a marker of how well O2 is being delivered to the peripheral tissue. By action on mitochondrial KATP channels, levosimendan causes preconditioning ,thereby reducing the extent of myocardial ischemia-reperfusion injury.[17-19] Labiola C et al[7] conducted a study to evaluate whether benefits of levosimendan ,used to treat acute exacerbation of chronic heart failure, could be extended to patients with low output syndrome following cardiac surgery. They used loading dose of 12 ug/kg over 10 mins followed by 0.1 ug/kg/min for 12 hrs and showed that cardiac index, stroke volume, was significantly increased but systemic vascular resistance and PCWP was significantly low. De Hert, et al[20] have recently shown that Levosimendan in combination with dobutamine maintained stroke volume better than milrinone, in combination with dobutamine in cardiac surgery patients with a preoperative ejection fraction <30%. Tritapepe et al[21] showed that lower postoperative Troponin-I levels with levosimendan prophylaxis . Baggish and colleagues[22] showed a positive correlation between postoperative troponin T levels and intensive care length of stay. Our study demonstrates that prophylactic levosimendan provides positive inotropy and vasodilatation and better tissue perfusion with neutral effect on O2 consumption as manifested by significantly higher SVO2 and SCVO2 in post CPB(SVO2-78.22±4.2, SCVO2-75.24±4.53) and ICU period (SVO2-at T0-70.11±5.27, T6- 74.83±3.98, T12-68.74±4.72,T24-73.8±4.43) and (SCVO2 at T0-71.94±4.69,T6-77.28±3.64, T12-67.72±3.81, T24-68.6±3.9) as shown in [Table 2], IUkkonen H et al also showed less O2 consumption by levosimendan in their study.[23] It provides better hemodynamics and significantly lower postoperative Troponin-I level after 24 hrs postop period (2.1±0.43) than milrinone

(4.83±3.02)as in [Table 3] denoting less myocardial injury. [Table 4] showing significantly less inotropes uses (dobutamine-4,053 ±1,957, less ICU stay as shown in table-4 than prophylactic milrinone infusion. Levosimendan protect the ischemic myocardium when administered before and during myocardial ischemia[24]. Momeni et al found in their study that myocardial oxygen demand is significantly less in levosimendan gr. Experimental reports have also observed increased blood flow with levosimendan to various tissues including the gastric mucosa, renal medulla, small intestine, and liver.[25,26] Levosimendan has an active metabolite which has similar hemodynamic effects [10-12] and has a long elimination half life of around 70 to 80 hours. [12] This can be an explanation of its positive hemodynamic effects lasted even after the 24-hour infusion, Levosimendan may constitute a cost effective option as it decreases significantly ICU and hospital stay and consequent risk of complications after open-heart surgery in high risk patients with compromised cardiac function.

CONCLUSION

Levosimendan is a safe and efficient choice in the prophylaxis of low-output syndrome during and after open heart surgery with compromised heart. The unique inotropic and cardio-protective property of levosimendan confirms its superiority.

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