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A Prospective Equivalence Study Of Milrinone And Levosimendan In Patients With Left Ventricular Systolic Dysfunction Undergoing Elective Coronary Revascularization Without Cardiopulmonary Bypass

Nageswara Rao. Pragada[1], Jayanth. Aveek[2].
[1] *Dept of Cardiac Anaesthesia, Amrita Institute of Medical Sciences, Kochi, India*
[2] *Dept of Cardiac Anaesthesia, Amrita Institute of Medical Sciences, Kochi, India*

ABSTRACT:
Objective: *To demonstrate the equivalence of milrinone and levosimendan in the immediate postoperative period in patients with left ventricular systolic dysfunction.*
Design & Setting: *A prospective equivalence study from December 2017 to December 2019 at Amrita Institute of Medical Sciences, Kochi. Patients undergoing OPCAB with EF <40% were included in this study.*
Participants & Intervention: *Randomization done intraoperatively on table or in the ICU. Patients were received either Levosimendan bolus dose of 6 µg kg $^{-1}$. given over 1 hr. followed by dosage of 0.05 to 0.2 µg kg $^{-1}$ min $^{-1}$ or Milrinone 30 µg kg $^{-1}$ bolus over 1 hour followed by dosage of 0.3 to 0.5 µg kg $^{-1}$ min $^{-1}$. The primary outcome was 30-day mortality.*
Results: *Total 78 patients were randomized into either milrinone (39) or levosimendan (39) group as intention to treat analysis. 40 patients received the drug either levosimendan or milrinone as per protocol. There was no significant difference in the 30-day mortality between the levosimendan and milrinone group, (39 patients {7.7%} and 39 patients {2.6%}, respectively; P=0.615).*
Conclusion: *we conclude that there are no clinically significant differences between the use of levosimendan and milrinone in patients with ischemic cardiomyopathy undergoing OPCAB.*
Key Word*: Milrinone, Levosimendan, Off pump coronary artery bypass surgery, Ischemic cardiomyopathy.*

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I. INTRODUCTION

Off pump coronary artery bypass (OPCAB) is a widely used revascularization technique, particularly in the Indian subcontinent[1].

Milrinone improves cardiac function with no significant increase in myocardial oxygen consumption and its myocardial oxygen consumption is lower compared to that of dobutamine. It's positive effect on myocardial contractility and coronary blood flow with minimal increase in heart rate and myocardial oxygen consumption make milrinone a possible inotropic agent of choice for patients undergoing OPCAB[2].

Levosimendan has been used to demonstrable efficacy in the prevention of low cardiac output syndrome after cardiac surgery[3]. Milrinone and levosimendan have not, to our knowledge been compared head to head in this clinical setting. It is therefore necessary to obtain a head to head comparison of both these common agents so as to demonstrate equivalence or otherwise.

II. METHODS

This prospective randomized controlled study was conducted at Amrita Institute of Medical Sciences, Kochi between December 2017 to December 2019. The Trial was registered on clinicaltrial.org, trial number is awaited. The study protocol was approved by the Institutional Review Board and Ethics Committee of the institute and written informed consent was obtained from all patients.

Selection and Description of participants:

Consenting patients undergoing off pump CABG surgery with moderate or severely reduced left ventricular ejection fraction (<40% as diagnosed on preoperative TTE were included).Exclusion criteria were patients with a baseline blood systolic pressure < 90 mm Hg, patients with proven sepsis (bacterial or fungal) in the preceding 7 days before the procedure, dialysis dependent renal failure, Child – Pugh Class B or C liver disease, exposure to either drug in the preceding 30 days prior to surgery, pericardial disease, inability to place a

Swan Ganz Continuous Cardiac output catheter due to technical or patient considerations, contraindications to the use of a transesophageal echocardiography probe.

Technical Information:

Baseline transthoracic echocardiography, demographic biochemical and relevant clinical data were captured. Patients then underwent randomization if they met the enrollment criteria. Patients were randomized on an intention to treat (ITT) to either levosimendan (L) or milrinone (M). Levosimendan was administered at a bolus dose of 6 µg kg $^{-1}$ min $^{-1}$. given over 1 hr. followed by minimum dosage of 0.05 µg kg $^{-1}$ min $^{-1}$ and maximum dosage of 0.2 µg kg $^{-1}$ min $^{-1}$. Milrinone was administered first as 30 µg kg $^{-1}$ bolus over 1 hour followed by minimum dosage of 0.3 µg kg $^{-1}$ min $^{-1}$. and maximum dosage of 0.5 µg kg $^{-1}$ min $^{-1}$. The study drug was infused for maximum of 48 hours. The infusion could be stopped earlier in case of favourable clinical and hemodynamic parameters.

The primary outcome of the trial was 30-day mortality. We also collected data on the following outcomes: need for renal replacement therapy or AKI based on the KDIGO guideline, need for advanced mechanical circulatory support, post-operative infections, atrial fibrillation requiring therapy, blood transfusions, low cardiac index <2.1 incidence, requirement of Inotropes.

In our equivalence study, we expected the proportion of mortality in both the groups as 3.5% each based on the CHEETAH study (Landoni 2017)[4]. Using this proportion with alpha error 5% and power 80%, we calculated that, a sample of 53 patients per group is needed. Total 78 patients were included in the study and 39 patients received the drug either levosimendan or milrinone as per protocol. All 78 patients were randomized into 2 groups either milrinone having 39 patients or levosimendan having 39 patients as intention to treatment.

Statistics:

Statistical analysis was done using IBM SPSS 20.0 (SPSS Inc, Chicago, USA). For all the continuous variables, data was described as mean ± SD, and for categorical variables as percentage. To compare the mean difference of numerical variables between groups, independent two sample 't' test was applied for parametric data and Mann Whitney u test for non-parametric data. To compare the pre- and post-operative Scores, paired t test was applied for parametric and Wilcoxon signed –rank test for nonparametric data respectively. The chi square with Fisher's exact test was used to describe the difference between groups in respect of categorical variables. A p-value < 0.05 was considered as statistically signific

III. RESULTS

A total of 78 patients were recruited into this study beginning January 2018 and ending December 2019 on an intention to treat basis. Only 40 patients did actually receive study medication as the remaining patients did not receive study medication as prescribed in the protocol either due to stability of cardiac index or because they did not receive the study drug for a minimum of 6 hours; the most common cause for cessation of drug was hemodynamic stability. Therefore, the results are presented a. as per protocol and b. intention to treat analysis.

PER PROTOCOL ANALYSIS

Follow up was complete in all the patients who received study drug. The study groups did not differ in demographic characteristics or baseline ejection fraction (EF)The mean value of EF before giving the drug in the milrinone (28.2) and levosimendan (31.2) were not significantly different. (p=0.15). Post administration of study drug and end of revascularisation in the OR the EF between the two groups was similar milrinone (31.9±5 %) and levosimendan (35± 4%), p= 0.08.At 30 days, there were 3 deaths (15% of patients) in the levosimendan group and 1 death (5% of patients) in the milrinone group with (p=0.60).

The mean duration of ICU stay in milrinone group was 4.5 days and in levosimendan group was 3.65 days (p=0.65). The mean duration of hospital stay in milrinone group was 10 days and in levosimendan group was 10.88 days. This was not statistically significant between the two groups with a P value 0.479 (TABLE NO.2 AND 3).

INTENTION TO TREAT ANALYSIS

Follow up was complete in all the patients who included in this study. The study groups did not differ in demographic characteristics or baseline ejection fraction (EF). The mean value of EF before giving the drug in the milrinone (35.46) and levosimendan (35.87) were not significantly different. (p=0.73

At 30 days, there were 3 deaths (7.7% of patients) in the levosimendan group and 1 death (2.6% of patients) in the milrinone group with (p=0.61).

The mean duration of ICU stay in milrinone group was 3.97 days and in levosimendan group was 4.05 days (p=0.64). The mean duration of hospital stay in milrinone group was 11.42 days and in levosimendan group

was 13.56 days. This was not statistically significant between the two groups with a P value 0.19 (TABLE NO.4 AND 5.).

TABLES

Table 1: COMPARISON OF DEMOGRAPHIC DATA BETWEEN THE GROUPS IN PER PROTOCOL ANALYSIS (n=40)

VARIABLES	MILRINONE			LEVOSIMENDAN			P value
	n	Mean	SD	N	Mean	SD	
Age	20	58.85	7.07	20	59.35	7.31	0.892
Height	20	162.85	9.16	20	160.70	6.48	0.315
weight	20	59.94	10.59	20	63.45	11.65	0.470
Body Surface Area	20	1.64	0.20	20	1.65	0.15	0.818

Table 1 shows demographic variables including age, height, weight, body surface area, were similar between the two groups with P >0.05, statistically not significant.

Results of Analysis of Primary and Secondary Outcomes in per protocol analysis(n=40):

Table 2: Comparison of Categorical Variables

VARIABLE	GROUPS		p – Value
	MILRINONE n (%)	LEVOSIMENDAN n (%)	
30day mortality			
No	19 (95)	17 (85)	0.605
Yes	1 (5)	3 (15)	
AKI incidence			
No	19 (95)	17 (85)	0.605
Yes	1 (5)	3(15)	
CI <2.1			
No	12(60)	13(65)	1.000
Yes	8 (40)	7 (35)	
Dialysis			
No	20(100)	17(85)	0.231
Yes	0(0)	3(15)	
PRBC transfusion			
No	10(50)	9(45)	1.000
Yes	10(50)	11(55)	
Post op infections			
No	18(90)	19(95)	1.000
Yes	2(10)	1(5)	
AF requiring therapy			
No	19(95)	16(80)	0.342
Yes	1(5)	4(20)	
Positive ICU fluid balance			
No	16(80)	17(85)	1.000
Yes	4(20)	3(15)	
ECMO support			
No	20(100)	19(95)	1.000
Yes	0(0)	1(5)	

Table 2 shows the primary outcome 30day mortality and secondary outcomes including AKI incidence, incidences of low CI <2.1, requirement of dialysis, PRBC transfusion, post op infections, AF, ICU fluid balance, ECMO support were similar in both groups with P >0.05.

Figure No.1: Comparison of 30day Mortality Between the Groups

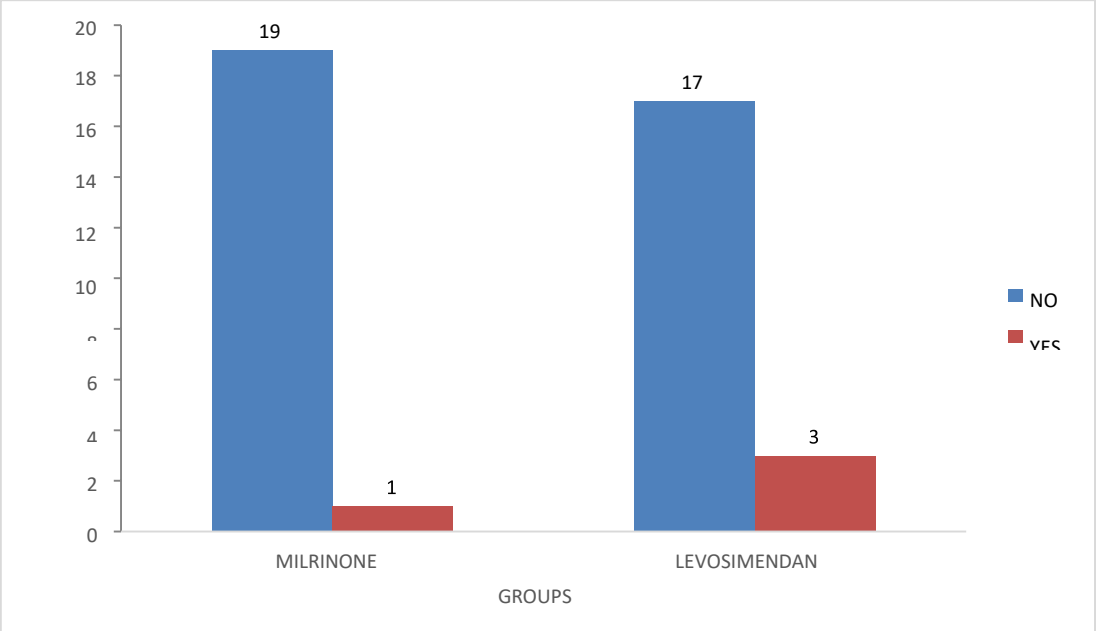

Figure 1 shows Out of 20 patients in MILRINONE group 1(5%) death within 30 days. In 20 patients of LEVOSIMENDAN group 3(15%) deaths within 30 days. Comparison of 30 days mortality between groups was found to be similar with p value 0.605.

Table: 3
Comparison of Continuous Variables

VARIABLES	MILRINONE			LEVOSIMENDAN			P value
	n	Mean	SD	n	Mean	SD	
ICU stay	20	4.55	4.71	20	3.65	0.98	0.640
Hospital stay	20	10	2.62	20	10.88	4.01	0.470
Duration of ventilation	20	43	131.37	20	25.8	34.47	0.342
Inotrope score on day 0	20	119.29	108.93	20	155.22	69.61	0.070
Inotrope score on day 1	20	185.3	163.31	20	184.9	143.52	0.842

Table 3 shows the secondary outcome variables including ICU stay, hospital stay, ventilation duration, requirement of inotrope score on day 0 and day 1 were similar between the two groups with P >0.05, not statistically significant.

Results of Analysis of primary and secondary outcomes in intention to treat analysis (n=78):
PRIMARY OUTCOME:

Table No. 4
Comparison of 30day Mortality Between the Groups

30 DAY MORTAALITY	Groups		p value
	MILRINONE n=39 (%)	LEVOSIMENDAN n=39 (%)	
NO	38 (97.4%)	36 (92.30%)	0.615
YES	1 (2.6%)	3 (7.7%)	

Figure No.2: Comparison of 30day Mortality Between the Group

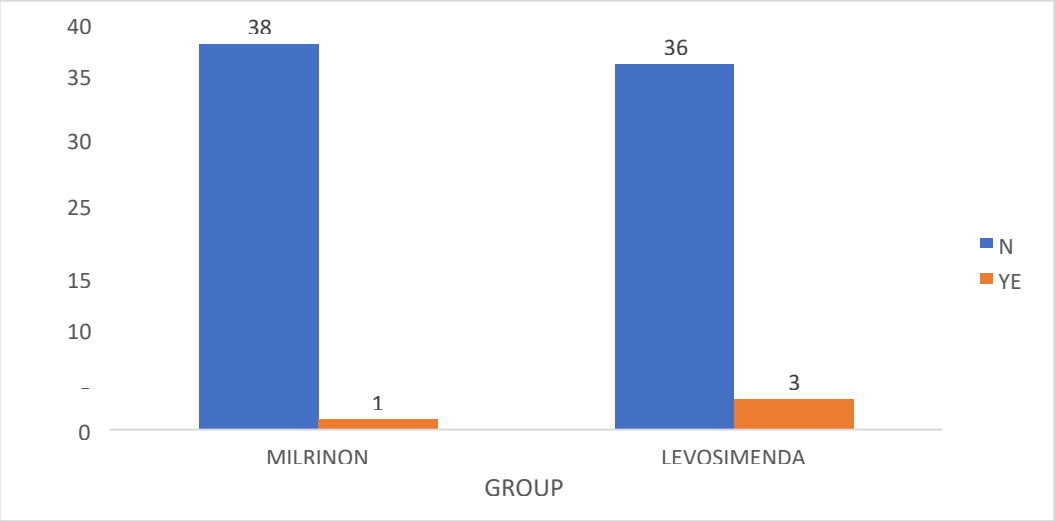

Table 4 and figure 2 shows out of 39 patients in MILRINONE group 1(2.6%) death within 30 days. In 39 patients of LEVOSIMENDAN group 3(7.7%) deaths within 30 days. Comparison of 30 days mortality between groups was found to be statistically not significant with p value 0.615.

SECONDARY OUTCOMES:

Table 5
Comparison of Continuous Variables

VARIABLES	MILRINONE			LEVOSIMENDAN			P value
	n	Mean	SD	n	Mean	SD	
ICU stay	39	3.97	3.50	39	4.05	3.66	0.640

Hospital stay	39	11.42	3.58	39	13.56	9.29	0.192

Table 5 shows the mean duration of ICU stay in milrinone group was 3.97 days and in levosimendan group was 4.05 days (p=0.64). The mean duration of hospital stay in milrinone group was 11.42 days and in levosimendan group was 13.56 days. Thiswas not statistically significant between the two groups with a P value 0.19.

IV. DISCUSSION

The authors of this study attempted to perform a head to head comparison of milrinone with levosimendan in a high-risk group of patients with ischemic cardiomyopathy undergoing OPCAB. The Western literature is largely concordant on OPCAB offering inferior outcomes such as lesser completeness of revascularization and increases chances of requiring reintervention (Shroyer 2017)[5]. However, the Indian subcontinent still anecdotally reports a high use of OPCAB but, with a large gap in the published literature on outcomes from this geographical region.

Other authors have used levosimendan on a prophylactic basis (Tritapepe 2009)[6] and demonstrated that when used pre- emptively this drug decreased mortality, eased separation from cardiopulmonary bypass and reduced the need for supplemental vasoactive medication postoperatively. However, in our study we used the trial medications only if there was a period of CI< 2.1 L min^{-1} m^2 for a continuous period lasting 30 minutes or more and patients were deemed to have received adequate dosing to be included in the per protocol analysis only if they received a bolus and infusions for 6 hours or more at any time during their perioperative course. This, we deemed reasonable as levosimendan, in particular has a short kinetic half-life and only, OR 1896 its long acting metabolite ensures durability of its hemodynamic and other pluripotent effects (Pathak 2013)[7].

Although our study was not designed to test this proposition it was found that nearly half of the patients studied did not need inodilatory therapies on a routine basis. We also believe that this is indeed a valid approach since all of these medications also have important side effects such as arrhythmogenicity (Flevari 2006, Stump 200)[8-9] and, at least reading from the wider heart failure literature do not improve survival for milrinone in ischemic cardiomyopathy (Felker 2003)[10] but putatively could produce symptomatic improvement in some but not all reviewed literature (Altenberger 2018)[11].

Over all there was no difference in the primary outcome deemed to be of statistical significance (30-day mortality rates of 2.2% and 7.7% for levosimendan vs milrinone respectively, p=0.62). The overall mortality in this cohort however was an improvement over previously reported data from our center (Jose 2019)[12] but this published cohort was a mixed cohort of patients undergoing CABG using both ONCAB and OFFCAB modalities. The overall mortality in the study population was comparable to that described from other health systems which use OPCAB as the primary modality for CABG (Li 2017)[13] but somewhat higher than some of the age groups reported from the STICH registry (Petrie 2016)[14] and very similar to the study and placebo groups in the LICORN trial (Cholley 2017)[15].

Within the constraints of our study we conclude that there are no clinically significant differences between the use of levosimendan and milrinone when used to support the circulation in patients with ischemic cardiomyopathy undergoing OPCAB.

V. CONCLUSION

A total of 78 patients with ischemic cardiomyopathy were recruited into this study which attempted to investigate the equivalence between two popular inodilator drugs in patients undergoing off pump coronary artery bypass surgery with a diagnosis of preoperative ischemic cardiomyopathy. A significant proportion of patients did not receive the study medication as envisaged. Nevertheless, there was no difference in the primary outcome (30-day mortality) between the two groups in the per protocol and in the summary intention to treat analysis. There was also no significant differences in the length of intensive care unit and hospital stay or in the postoperative course of acute kidney injury, adjunct use of vasoactive medication, ejection fraction and improvement in EF or the wall motion score index.

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