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Original Article

Anaesthesia Section

Comparison of Levosimendan, Milrinone and Dobutamine in treating Low Cardiac Output Syndrome Following Valve Replacement Surgeries with Cardiopulmonary Bypass

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ABSTRACT

Introduction: Low Cardiac Output Syndrome (LCOS) following Cardiopulmonary Bypass (CPB) is common and associated with increased mortality. Maintenance of adequate cardiac output is one of the primary objectives in management of such patients.

Aim: To compare Levosimendan, Milrinone and Dobutamine for the treatment of LCOS after CPB in patients who underwent valve replacement surgeries.

Materials and Methods: Sixty eligible patients meeting LCOS were allocated into three treatment groups: Group A-Levosimendan (loading dose 10µg/kg over 10 minutes, followed by 0.1µg/kg/min); Group B-Milrinone (loading dose 50 mcg/kg over 10 minutes followed by 0.5mcg/kg/min) and Group C-Dobutamine @ 5µg/kg/min to achieve target cardiac index (CI) of > 2.5 L/min/m^2. In case of failure, other drugs were added as required. Hemodynamic parameters were monitored using EV1000TM clinical platform till 30 minutes post CPB. INSTAT software was used for statistics and $p<0.05$ was considered significant.

Results: The mean±standard deviation of time taken by Dobutamine, Levosimendan and Milrinone to bring the CI to target were 11.1±8.79, 11.3±6.34 and 16.62±9.33 minutes respectively ($p=0.064$). Levosimendan was equally effective in increasing and maintaining adequate CI as compared to Dobutamine ($p>0.05$). Levosimendan and Milrinone increased MAP (Mean Arterial Pressure) equally while Dobutamine was more effective as compared to both Levosimendan and Milrinone 20th minute onwards ($p<0.01$). Milrinone was less effective in increasing the stroke volume as compared to Dobutamine and Levosimendan while Dobutamine and Levosimendan were equally effective. There was no difference in the HR (Heart Rate) achieved with all these three drugs.

Conclusion: Levosimendan is equally effective to Dobutamine and better than Milrinone for the treatment of LCOS following CPB in patients undergoing valve replacement surgeries.

Keywords: Cardiac output/therapy, Cardiac index, Heart valve/surgery, Haemodynamics/drug effects, Low cardiac output

INTRODUCTION

Maintenance of adequate cardiac output is one of the primary objectives while managing patients undergoing cardiac surgery as it is one of the major components of oxygen delivery to the tissues. Myocardial dysfunction and circulatory impairment following Cardio Pulmonary Bypass (CPB) is very common [1]. Pre-operative cardiac problems along with the events related to cardiac surgery and CPB leads to the Low Cardiac Output Syndrome (LCOS) in many patients. Circulatory supports by pharmacological means are often required to treat this LCOS and many agents have been used time to time for treatment but ideal agent is yet to be found [2].

Levosimendan is a relatively new cardioprotective, positive inotropic agent having Adenosine Triphosphate (ATP) dependent potassium-channel-opening and calcium sensitization of contractile proteins. It has mild PDE (phosphodiesterase) inhibitory action and unlike other inotropic agents, levosimendan improves cardiac performance without activating the sympathetic nervous system [3]. It has been approved for management of acutely decompensated heart failure and may offer a solution to this unmet need. It has also been well recommended by experts for perioperative use in cardiac surgical patients with myocardial dysfunction [4]. LCOS is an acute form of heart failure and a major cause of perioperative death in patients undergoing cardiac surgeries [5]. It is reasonably defined as CI (Cardiac Index) ≤ 2.2 L/min/m^2 of BSA (Body Surface Area) with pulmonary capillary wedge pressure ≥18 mmHg, MAP ≤50 mmHg, and systemic vascular resistance ≥1,500 dynes/sec/cm^{-5} along with evidence of organ dysfunction (e.g. elevated lactate or urine output under 0.5 ml/hour for more than 1 hour) [6]. As urine output is usually higher in cardiac surgeries and lactate is likely to be high after CPB, in the present study LCOS was diagnosed with CI ≤ 2.2 L/min/m^2 of BSA with central venous pressure ≥18 mmHg and MAP ≤ 50 mmHg.

Inotropic drugs like PDE inhibitors and beta-adrenergic agonists are used for both separation from CPB and treatment of LCOS. However, despite a wide range of available inotropic agents, best suitable agent for the treatment of LCOS post CPB is still lacking [2]. Considering the beneficial effects of Levosimendan, this drug has become an interest to the cardiologist, intensivists and cardiac anesthesiologists. The present study was aimed to compare the efficacy of Levosimendan with Milrinone and Dobutamine in the treatment of LCOS in patients who underwent valve replacement surgeries with CPB using the haemodynamic responses as an observational variable.

MATERIALS AND METHODS

The present study was conducted in a tertiary care referral centre of North East India during the period from March 2014 to March 2016. The Institutional Ethical Committee approval was obtained (No. P-172/12/83). Patients of either sex, aged between 15 to 65 years, who underwent elective valve replacement surgeries with CPB and not having Pre-operative decompensated heart failure and

renal failure were eligible for the study. Informed and written consent from the agreed eligible patients were obtained.

Sixty consecutive patients who developed LCOS {defined as CI≤ 2.2 L/min/m^2 of BSA with central venous pressure ≥18 mmHg and mean arterial pressure (MAP) ≤50 mmHg [6]} were included for comparison and analysis. Alternate eligible patients (e.g., 1, 4, 7... in one; 2, 5, 8... in another and 3, 6, 9... in the other group) were allocated into three treatment groups: Group A-Levosimendan (loading dose 10μg/kg over 10 minutes, followed by 0.1μg/kg/min); Group B-Milrinone (loading dose 50mcg/kg over 10 minutes followed by 0.5mcg/kg/min) and Group C-Dobutamine @ 5 μg/kg/min. All drugs were started at the end of CPB and CI of > 2.5 L/min/m^2 of BSA was targeted. In case of failure to achieve the target in 30 minutes other drugs were added as required. Haemodynamic parameters were monitored using EV1000™ clinical platform of Edwards Lifesciences™ Corporation, USA. The clinical platform was kept ready and monitoring was started after removal of aortic cross clamp. Post CPB haemodynamic data of 1, 2, 3, 5, 10, 15, 20, 25 and 30 minutes were noted and a master chart (Microsoft Excel 2007 from Microsoft Corporation, USA) was prepared. The collected data was analysed statistically by one-way-ANOVA with post-hoc test for pairwise comparisons if the results were found significant and unpaired t-test using INSTAT software (GraphPad software, Inc, La Zolla, CA, USA).

RESULTS

The patients of all the three study groups were similar with regard to demographic parameters (p>0.05). The gender and Pre-operative symptomatic/physical class distribution as per American Society of Anesthesiologists (ASA) and New York Heart Association (NYHA) were also not statistically different [Table/Fig-1]. The duration of myocardial insult with regard to CPB and aortic cross clamp were also not different. The mean±standard deviation (SD) CPB time for Dobutamine, Levosimendan and Milrinone group were 92.05±14.09, 89.65±17.14 and 93.15±14.43 minutes (p= 0.761) while for aortic cross clamp were 57.35±13.70), 56.85±13.44 and 63.8±13.47 minutes (p= 0.181) respectively.

Dobutamine was the fastest {(mean±SD (95% confidence interval) time: 11.1±8.79 (6.98 – 15.21 minutes} to achieve target CI of ≥ 2.5 L/m^2 BSA as compared to Levosimendan and Milrinone 11.3±6.34 (8.33 – 14.26) and 16.62±9.33 (12.15 – 20.99) minutes respectively, but the difference was not statistically significant (p=0.064).

The mean CI achieved by Dobutamine was consistently higher from 5th minute post CPB onwards as compared to both Levosimendan and Milrinone [Table/Fig-2]. However; compared to Levosimendan, though Dobutamine at 30 minutes post CPB could achieve higher mean CI, the difference was not statistically significant (4.36±1.60 versus 3.57±1.04 L/m^2 BSA, p =0.0714), but the difference remained statistically significant from 20th minutes post CPB onwards when compared to Milrinone (4.36±1.60 versus 3.14±0.63 L/m^2 BSA) [Table/Fig-3]. There was no statistical difference between the mean CI achieved by Levosimendan and Milrinone during 30 minutes post CPB (lowest p= 0.0592)

At 30 minutes post CPB, Dobutamine could achieve the maximum rise in the MAP as compared to Levosimendan and Milrinone (p=0.0004). However, there was no significant difference in the heart rate achieved with Dobutamine, Levosimendan and Milrinone during the post bypass 30 minutes [Table/Fig-4]. On the other hand, from 10 minutes post CPB onwards SV (stroke volume) achieved with Dobutamine was significantly higher (p < 0.01) than both Levosimendan and Milrinone [Table/Fig-4].

DISCUSSION

Parameter	Dobutamin		Levosimendan		Milrinone		p-value
	(%) or Mean (SD)	95 % CI	n (%) or Mean (SD)	95 % CI	n (%) or Mean (SD)	95 % CI	
Male Female	8 (40%) 12 (60%)	- -	12 (60%) 8 (40%)	- -	11(55%) 9 (45%)	- -	>0.99
ASA III IV	3.15 (0.36) 17 (85%) 3 (15%)	2.97 – 3.32 - -	3.20 (0.41) 16 (80%) 4 (20%)	3.00 – 3.39 - -	3.15 (0.36) 17 (85%) 3 (15%)	2.97 – 3.32 - -	0.875
NYHA III IV	3.1 (0.30) 18 (90%) 2 (10%)	2.95 – 3.24 - -	3.05 (0.39) 18 (90%) 2 (10%)	2.86 – 3.23 - -	3.1 (0.30) 18 (90%) 2 (10%)	2.95 – 3.24 - -	0.865
Age (years) Weight (Kg) Height (inch) BMI	41.2 (11.7) 50.55 (8.74) 65.05 (3.63) 18.59 (2.55)	35.68 – 46.71 46.45 – 54.64 63.34 – 66.75 17.39 – 19.78	37.05 (13.62) 53.75 (14.22) 63.15 (4.51) 20.65 (5.47)	30.67 – 43.42 47.09 – 60.40 61.03 – 65.26 18.09 – 23.22	34.45 (14.5) 50.4 (14.77) 62 (3.50) 18.15 (2.65)	27.65 – 41.24 43.48 – 57.31 60.35 – 63.34 16.90 – 19.39	0.579 0.645 0.107 0.093

[Table/Fig-1]: Demographic and physical status parameters expressed in absolute number and percentage scale and analysed using one-way-ANOVA. (ASA-American Society of Anesthesiologists, NYHA- New York Heart Association, BMI – Body Mass Index, SD- standard deviation, CI- confidence interval).

Cardiac Index (post bypass)	Dobutamine		Levosimendan		Milrinone		p-value
	Mean (SD)	95 % CI	Mean (SD)	95 % CI	Mean (SD)	95 % CI	
1 Minute	1.41 (0.65)	1.10 – 1.71	1.36 (0.41)	1.17 – 1.55	1.21 (0.52)	0.96-1.4	0.496
2 Minutes	1.66 (0.75)	1.30 – 2.02	1.64 (0.60)	1.35 – 1.92	1.41 (0.48)	1.18 – 1.63	0.370
3 Minutes	1.95 (0.84)	1.55 – 2.35	1.98 (0.49)	1.74 – 2.21	1.86 (0.84)	1.52 – 2.20	0.864
5 Minutes	2.64 (1.34)	2.01 – 3.26	2.33 (0.73)	1.98 – 2.68	2.17 (0.91)	1.74 – 2.59	0.348
10 Minutes	3.08 (1.25)	2.49 – 3.66	2.6 (0.746)	2.25 – 2.95	2.37 (0.90)	1.94 – 2.79	0.078
15 Minutes	3.23 (1.25)	2.64 – 3.81	2.89 (0.76)	2.53 – 3.24	2.62 (0.87)	2.20 – 3.03	0.156
20 Minutes	3.55 (1.25)	2.96 – 4.13	3.15 (0.91)	2.72 – 3.58	2.70 (0.90)	2.28 – 3.13	0.043
25 Minutes	4.14 (1.26)	3.54 – 4.73	3.33 (0.90)	2.91 – 3.75	2.92 (0.25)	2.80 – 3.04	0.0003
30 Minutes	4.36 (1.60)	3.61 – 5.11	3.57 (1.04)	3.07 – 4.06	3.14 (0.63)	2.84 – 3.43	0.005

[Table/Fig-2]: Cardiac index with time compared using one-way-ANOVA with post-test. (SD- standard deviation, CI- confidence interval).

CI (post CPB)	Milrinone		Dobutamine@	Levosimendan	
	p-value	Mean (SD)	Mean (SD)	Mean (SD)	P-value
1 minute	0.3071	1.21(0.52)	1.41 (0.65)	1.36 (0.41)	0.9616
2 minute	0.2124	1.41(0.48)	1.66 (0.75)	1.64 (0.60)	0.9089
3 minute	0.7222	1.86 (0.73)	1.95 (0.84)	1.98 (0.49)	0.9101
5 minute	0.2026	2.17(0.91)	2.64 (1.34)	2.33 (0.73)	0.3785
10 minute	0.0471	2.37(0.90)	3.08 (1.25)	2.6 (0.746)	0.1496
15 minute	0.0826	2.62 (0.87)	3.23 (1.25)	2.89 (0.76)	0.3068
20 minute	0.0198	2.70 (0.90)	3.55 (1.25)	3.15 (0.91)	0.2628
25 minute	0.0002	2.92 (0.25)	4.14 (1.26)	3.33 (0.90)	0.0265
30 minute	0.0030	3.14 (0.63)	4.36 (1.60)	3.57 (1.04)	0.0714

[Table/Fig-3]: Cardiac Index (CI) of Levosimendan and Milrinone with time compared with Dobutamine @(taking it as standard) analysed using unpaired t-test. (CPB- cardiopulmonary bypass, SD- standard deviation).

Parameter	Time (post CPB)	Dobutamine		Levosimendan		Milrinone		p-value
		Mean (SD)	95 % CI	Mean (SD)	95 % CI	Mean (SD)	95 % CI	
Mean Arterial Pressure (mmHg)	1 minute	45.5 (14.97)	38.49 – 52.51	43.35 (12.0)	37.72-48.97	43.45 (11.59)	38.02-48.87	0.839
	5 minute	48.85 (15.24)	41.71 – 55.98	45.0 (12.10)	39.33-50.66	46.15 (13.75)	39.71– 52.58	0.663
	10 minute	64.0 (15.51)	56.74 – 71.26	55.35 (17.34)	47.23-63.46	53.15 (14.09)	46.55– 59.74	0.078
	20 minute	72.05 (13.24)	65.85 – 78.25	60.40 (20.03)	51.02-69.77	57.0 (13.07)	50.88-63.11	0.010
	30 minute	76.9 (14.26)	70.22 – 83.57	63.90 (13.01)	57.81-69.98	59.2 (13.4)	52.92– 65.47	0.0004
Heart Rate (beats per minute)	1 minute	62.47 (29.55)	48.22– 76.72	74.70 (26.62)	62.23-87.16	62.5 (24.62)	50.97 – 74.02	0.219
	5 minute	66.45 (29.76)	52.52– 80.37	74.45 (26.45)	62.07-86.82	66.35 (24.37)	54.94 – 77.75	0.551
	10 minute	71.7 (33.54)	55.99– 87.40	81.15 (18.68)	72.40-89.89	68.8 (24.28)	57.43 – 80.16	0.305
	20 minute	79.35 (29.36)	65.60– 93.09	83.35 (17.65)	75.08-91.61	75.95 (21.67)	65.80 – 86.09	0.606
	30 minute	87.9 (27.01)	75.25– 100.5	83.45 (15.93)	75.99-90.90	79.85 (19.22)	70.85 – 88.84	0.490
Stroke Volume (milliliters)	1 minute	32.3 (15.74)	24.93–39.67	27.15 (8.02)	23.39-30.90	25.3 (11.85)	19.75 – 30.84	0.184
	5 minute	54.9 (26.13)	42.66–67.13	48.5 (14.98)	41.48-55.51	40.9 (15.80)	33.50 – 48.29	0.087
	10 minute	62.3 (19.91)	52.97–71.62	49.15 (13.44)	42.85-55.44	43.35 (15.19)	36.24 – 50.46	0.002
	20 minute	62.05(23.15)	51.21–72.88	52.4 (13.39)	46.13-58.66	43.75 (12.32)	37.98 – 49.51	0.005
	30 minute	65.5 (15.20)	58.38–72.61	62.55 (15.58)	55.25-69.84	50.95 (15.94)	43.48 – 58.41	0.011

[Table/Fig-4]: Mean arterial pressure, heart rate and stroke volume with time compared using ANOVA (CPB- cardiopulmonary bypass, SD- standard deviation, CI- confidence interval).

The present study was designed to compare Levosimendan with Dobutamine and Milrinone in the treatment of LCOS in patients who underwent valve replacement surgeries with CPB and aortic cross clamp. All the three drugs were started after excluding and correcting any temperature, electrolytes and acid-base abnormalities.

In the present study, Dobutamine and Levosimendan were able to achieve target CI of 2.5 L/min/m^2 BSA in nearly equal mean±SD time of 11.1±8.79 versus 11.3±6.34 minutes respectively. Although the mean±SD time taken by Milrinone was higher 16.62±9.33 minutes, the differences were however statistically insignificant (p>0.05). There was no significant difference in the CI achieved with Dobutamine and Levosimendan (p>0.05) though there was significant difference in CI achieved between Dobutamine and Milrinone from 20th minute onwards. This finding is similar to the studies by Maria José Carmona et al., and Feneck RO et al., [7,8]. However, no significant difference in the CI achieved with Levosimendan and Milrinone was noted in the present study (p>0.05).

The CI achieved by Levosimendan and Dobutamine although were not statistically different, the absolute mean value was lower for Levosimendan as compared to Dobutamine. This finding has resemblance to the findings of Ravikumar Gandham et al., comparing Dobutamine and Levosimendan [9]. They found that the CI was low in Levosimendan group in the initial period when compared to Dobutamine. On the other hand, a randomized study comparing Dobutamine and Levosimendan in patients who had low cardiac output after CPB showed that both Dobutamine and Levosimendan improved the CI but the increase was significantly greater with Levosimendan at 24 hours [10]. The present study was unable to comment on this as the data collection was limited only to half an hour post CPB. Another multicentre open level randomized study comparing 60 patients with Milrinone and 60 patients with Dobutamine found that Dobutamine produced greater increases in cardiac index, heart rate and mean arterial pressure at 1 hour (p < 0.01) and the findings of the present study too supports this [7].

The present study found no significant difference in SV achieved with Dobutamine and Levosimendan (p>0.05) with both achieving almost equal SV at 30th minute. However, there was a significant difference (p<0.05) in SV achieved between Dobutamine and Milrinone from 5th minute onwards with Dobutamine being able to achieve higher SV as compared to Milrinone. Similar findings were also shown between Levosimendan and Milrinone from 20th minute onwards (p<0.05) with Levosimendan being able to achieve higher SV. These findings are similar to the findings of other multicentre randomized study [7]. Levosimendan combined with Dobutamine has shown to increase SV significantly more than Milrinone combined with Dobutamine in cardiac surgical patients with Pre-operative poor left ventricular function also [11]. This also indirectly indicates that Levosimendan is more effective in increasing SV than Milrinone and supports the finding of present study.

However, the present study did not find significant difference in the HR achieved with Levosimendan as compared to Dobutamine and Milrinone which is in contrast to the findings of other studies where Dobutamine was found to increase heart rate significantly as compared to Milrinone and Levosimendan (p>0.05) [7,9].

On the other hand, Dobutamine was able to achieve a higher MAP from 20th minute onwards as compared to Levosimendan and from

10th minute onwards as compared to Milrinone in the present study although no significant difference in MAP was achieved between Levosimendan and Milrinone. Few other studies have also found that Dobutamine as compared to Levosimendan increases MAP significantly from baseline [7,9,10].

The present study however is limited with the fact that all the drugs were started at the same point of time (after weaning off from CPB) while onset of action for Levosimendan and Milrinone is 5-10 minutes whereas it is 1-2 minutes for Dobutamine. This bias is likely to affect the finding of time taken to achieve target CI. However, it is unlikely to change the impression (i.e., Levosimendan is equally effective in treating LCOS as compared to Dobutamine) drawn in the present study.

CONCLUSION

The findings of the present study indicates that Levosimendan is equally effective to Dobutamine and probably better than Milrinone for the treatment of LCOS following CPB in patients undergoing valve replacement surgeries.

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