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A pre - post study to evaluate the clinical efficacy of levosimendan infusion in acute decompensated heart failure

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Abstract: *Background:* Heart failure with reduced ejection fraction is a prevalent condition associated with high mortality rates. Levosimendan, a calcium sensitizer and inodilator, has emerged as a promising agent for improving cardiac contractility. *Aims and Objectives:* The study aims to evaluate the clinical efficacy of 24-hour levosimendan infusion in acute decompensated HFrEF patients requiring inotropic support by comparing the pre and post ejection fraction and its effect on renal function testsand serum electrolytes. *Materials and methods:* It was a pre-post study conducted in Shifaa Hospital, Bangalore over 12 months among 50 HFrEF patients. After a baseline echo and blood test, Levosimendan was loaded at 12µg/kg over 10 min followed byinfusion of 0.1µg/kg/min for 24 hours; subsequentlyby a 2D-echo. *Results:* The mean pre-infusion EF was 31.49% and post-infusion EF was 34.16% and this improvement was found to be statistically significant ($p<0.001$). Among 50 patients, 86% had improvement in EF ranging from 0.13–10.7%. Out of which 32% had 0.1-2%, while 24%had 2-4% improvement in EF. There was a significant reduction in eGFR in 64% ($p<0.001$) but the serum electrolyte levels did not show any significant changes ($p>0.05$). *Conclusions:* There is a significant improvement in ejection fraction post levosimendan, but a significant reduction in eGFR with no significant effect on the serum sodium or potassium levels.

Keywords; Levosimendan, Heart failure, Inotrope, Decompensated

Introduction

Heart failure remains a leading cause of morbidity, mortality, and recurrent hospitalizations worldwide, with an estimated 64.3 million people affected globally. In comparison with the people of European ancestry, cardiovascular diseases affects Indians at least a decade earlier and in their most productive midlife years [1]. HFrEF, defined as a reduced left ventricular EF of ≤40%, represents a substantial proportion ofHF cases. This condition results from a variety of etiologies, including ischemic heart disease, hypertension(HTN) and cardiomyopathies [2].

While treatment strategies for HFrEF have advanced significantly, patients with persistently symptomaticHF despite the use of guideline-directed medical therapies remain a clinical challenge. Intravenous positive inotropic agents play an important role in the short-term management of these patients. β-Adrenergic agonists and phosphodiesterase inhibitors are the most commonly used agents, exerting a positive inotropic action primarily by increasing cAMP in cardiac myocytes [3].

Levosimendan is a novel agent with a dual mechanism of action developed for the treatment of ADHF. This agent sensitizes troponin C to calcium, thereby increasing the effects of calcium on cardiac myofilaments during systole and improving contraction at low energy cost and low calcium concentration, and therefore thissensitization declines during diastole, allowing improved diastolic relaxation. Unlike agents that act through adrenergic pathways which cause diastolic calcium overload and can impair myocardial relaxation that could result in the adverse effects [4]. Levosimendan may therefore be an important alternative for the treatment of ADHF patients.

Levosimendan also acts byincreasing the renal blood flow, vasodilatation and possess anti-inflammatory effects against tubular injury [4]. It causes vasodilation by opening ATP-sensitive potassium channels without increasing myocardial oxygen demand [5]. Levosimendan has been well tolerated in most patients, but common adverse effects reported are hypotension, headache, and dizziness secondary to the vasodilating properties [6]. Increased incidence of atrial fibrillation has also been associated with infusion of levosimendan compared with dobutamine [6]. So the present study aims to evaluate the clinical efficacy of 24 hour levosimendan infusion in ADHF patients requiring inotropic support by comparing the pre and post EF with the help of 2D-echo and adverse effects following infusion.

Material and Methods

Study Area: The study was conducted in department of general medicine in Shifaa hospital, Bangalore.

Study Duration: The study was conducted for a period of 12 months from JUNE 2023 to MAY2024

Study Population: The present study included 50 ADHF patients requiring inotropic support with an EF < 40%, admittedin Shifaa Hospital, Bangalore.

Study Design: A pre - post cross sectionalstudy.

Inclusion Criteria: ADHF patients

- Age >18 years
- Left ventricular ejection fraction (LVEF) < 40%

Exclusion Criteria:

- SBP < 85 mmHg
- Heart rate (HR) > 12Obpm,
- Serum potassium < 3.5 mmol/l
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- eGFR less than 30 ml/min/1.73 m2 (MDRD).

Methodology:

- On ICU admission, the patients will be screened to assess their eligibility and after taking a Signed Informed consent from patient, a detailed history and clinical examination will be done.
- An initial 2D-echo and Blood samples will be collected for the investigations as per the study proforma.
- They will receive Levosimendan infusion at an initial loading dose of 12µg/kg delivered over 10 min followed by a continuous infusion of 0.1µg/kg/min for 24 hours. A repeat2D-echo will be done after the 24-hour infusion of levosimendan to look at the change in EF.

Sample Size: According to study by C. Bergh et al. (2010) [7]. The mean change in PCWP (mmHg) and Heart rate (b.p.m.) at 24 hrs after giving Levosimendan were reported as -5.8 ±8.2 and 6.5 ±13.7 respectively. Assuming 5% level of significance and 80% power the required sample, sizes are 18 and 37 respectively. Therefore, the minimum required sample is 40 patients.

The following formula was used for sample size calculation.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \sigma^2}{d^2}$$

σ - Standard deviation of the difference; d - Expected mean difference between pre and post treatment; Z1-β - Z value for corresponding power; Z1-α/2 - Two-sided Z value for corresponding α.

Statistical Method: All the qualitative variables were summarized by frequency and percentages and all the quantitative variables were summarized by Mean, Median, Standard Deviation, and Interquartile range and reported with suitable statistical measures, depending on the shape of the data. The repeated measured variables were assessed by paired t-test if the distribution is normal otherwise by using Wilcoxon Signed Rank test. A P value <0.05 was considered statistically significant.

Ethics:

- Participants were explained about the study and informed consent was taken.
- Participation was voluntary.

- If the patient did not want to participate, no discrimination was made. He or she was given the standard of care

Results

The total study population was 50 HFrEF patients with age range from 38 years to 90 years with mean age of 65.56 ± 13.4years, of which 32 (64%) were male and 18 (36%) were female.

Out of the 50 patients, 47(94%) of them presented with the chief complaint of shortness of breath with 61.7% of them with NYHA 4 symptoms. Dry cough was the next most common symptom in 45(90%) of the patients followed by generalised weakness (80%), leg swelling (64%) and decreased urine output (16%). Among the 50 patients, 66% of the study population had habits, smoking being the most common with 52 % (n = 27) followed by pan chewing and alcohol.

Table-1: Distribution of Pre-infusion EF

Variable	Category	N	%
Pre infusion EF	16-20%	6	12
	21-25%	7	14
	26-30%	4	8
	31-35%	14	28
	36-40%	19	38
	Mean	31.49	
	SD	8.05	
	Range	15%-40%	

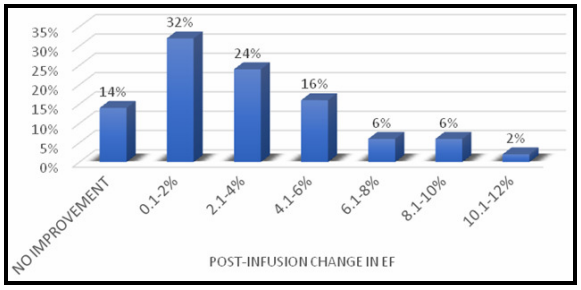
In our study, the pre-infusion EF ranged from 15-40%, of which the majority of the patients were in the 36-40% group and a mean EF of 31.49 ± 8.05 (Table-1).

Table-2: Distribution of Pre and post-infusion echo values

Variable	Period	N	MEAN	SD	MEDIAN	P-value(P T-test)
EF	Before	50	31.49	8.05	33.49	<0.001
	After	50	34.16	7.97	35.86	

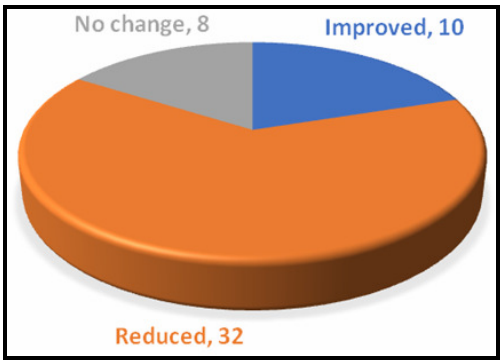
The mean of the pre-infusion EF was 31.49 ± 8.05 and post-infusion mean EF was 34.16 ± 7.97 and this improvement in EF was found to be statistically significant (p<0.001) (Table-2).

Fig-1: Distribution of Post -infusion change in EF



Among the study population, the mean post-infusion improvement in EF ranged from 0.13% upto 11%, with a mean of 2.94± 2.76 and majority falling in the 0.1-2%(n=16) and 2.1-4%(n=12) group. Out of the 50 patients, 76% (n=38) had HTN, 74% (n=37) had DM, 68% (n=34) had CAD and 14% (n=7) had CKD, but no significant relation between change in EF and presence of DM, HTN or CKD were found (Figure-1).

Fig2: Distribution of Post-infusion change in eGFR



The paired analysis between RFT values pre and post infusion showed a significant worsening of renal parameters post-infusion (p<0.001). There was a significant reduction in post-infusion eGFR values calculated using MDRD formula, with 32 out of 50 patients a mean eGFR reduction of 8.91±8.15. There was no change in potassium values for 68% (n=34), while 14% (n=28) had increase in values with a mean of 0.53 which was not found to be statistically significant. Out of 50 patients, 40% had decrease in post-infusion

sodium and 30% each had either increase or no change in values, but these changes were not found to be significant statistically (Figure-2).

Discussion

The present study is a pre-post study conducted among ADHF patients requiring inotropic support with an EF < 40%, admitted under Department of Medicine in Shifaa Hospital, Bangalore during period of over 12 months. It was conducted among 50 HFrEF patients who satisfied the inclusion and exclusion criteria, after obtaining informed consent. The patient's blood samples were collected and an initial 2D-echo was performed to get baseline EF. They received Levosimendan infusion at an initial loading dose of 12µg/kg delivered over 10 min followed by a continuous infusion of 0.1µg/kg/min for 24 hours. A repeat 2D-echo and blood sampling was done after the 24 hour infusion to look at the change in EF, RFT and SE values.

In the present study, the mean age was 62.56 years, which ranged between 38 and 90 years with the majority of them being male (64%). Studies indicate that HF patients in India are often younger compared to Western populations as reported by the Trivandrum Heart Failure Registry reported a mean patient age of 61.2 years, with ischemic heart disease identified as the leading cause in 72% of cases [8].

All 50 patients were given 24 hour infusion of levoisimendan without any adverse events or anaphylactic reactions. The primary aim was to study the change in EF pre and post-infusion.In our study, the pre-infusion EF ranged from 15-40%, of which the majority of the patients were in the 36-40% group [Table-1]. The mean EF significantly improved from 31.49 ± 8.05% to 34.16 ± 7.97% (p<0.001), demonstrating a statistically significant benefit [Table-2]. This is consistent with findings from the LIDO trial (2002), which demonstrated that levosimendan significantly improved CO and reduced PCWP compared to dobutamine, leading to better hemodynamic outcomes and lower 31-day mortality [4].

Post-infusion EF improvements varied among patients, with some showing minimal improvement, while others exhibited increases of up to 11%.Among the study population, 86% showed improvement with the majority (32%) exhibiting an EF increase of 0.1-2%. A smaller subset experienced a more pronounced improvement, with 6% showing an increase of 8-10% [Figure-1]. The Casino trial (2004) also highlighted similar variability. This suggests that certain patient subgroups may respond more favorably to levosimendan, potentially influenced by baseline myocardial function, cardiac reserve, and comorbid conditions [9].

While levosimendan is known to improve cardiac function, its effect on renal function is more controversial. In this study, serum creatinine and urea levels significantly increased post-infusion (p<0.001), while eGFR decreased from 61.4 ± 30.7 to 57.04 ± 32.8 (p=0.001). In our study, 32 patients (64%) experienced a reduction, with a mean decrease of 8.91 ± 8.15, while only 10 patients exhibited slight improvements [Figure-2]. This suggests a negative impact on renal function, potentially due to systemic vasodilation leading to renal hypoperfusion.

Similar findings have been reported in the REVIVE II [9] and LEVO-CTS trials [10], where renal impairment was observed post-infusion, especially in patients with pre-existing CKD. We need to also consider the concomitant use of diuretics during HF, which may be one of the reason for the worsening RFT values. These findings are consistent with the REVIVE II trial [9], which reported an increased risk of hypotension and worsening renal function. Similarly, the LEVO-CTS trial [11] (2017) found that levosimendan did not significantly These findings are consistent with the Revive II trial (2005), which reported an increased risk of hypotension and worsening renal function, reduce mortality or low CO syndrome in cardiac surgery patients but was associated with renal impairment in some cases [9].

In contrast, some studies including the LIDO [4] and Russlan trials [12] suggested potential reno-protective effects of levosimendan due to vasodilation of renal arteries. The variability in renal response across trials and our study suggests that patients with pre-existing CKD may be more vulnerable. This reinforces the

need for careful monitoring of renal function in high-risk patients receiving levosimendan therapy [10].

Electrolyte disturbances are common in HF patients receiving inotropic therapy. However, in this study, serum sodium and potassium levels did not show statistically significant changes post-infusion ($p>0.05$). While 20 patients exhibited a decrease in sodium levels (mean change: -2.6 mEq/L), 15 showed an increase (mean change: +3.46 mEq/L), and the remaining 15 had no change. Similarly, potassium levels increased in 14 patients, decreased in 2, and remained stable in 34, but the overall change was not clinically significant.

This stability in electrolyte levels contrasts with the CHEETAH trial [12] (2021), which reported higher rates of electrolyte disturbances in patients receiving levosimendan for septic shock-related cardiac dysfunction. The lack of major electrolyte disturbances in our study suggests that levosimendan may have a more favorable electrolyte profile compared to dobutamine, which is often associated with hypokalemia and arrhythmias. The presence of DM, HTN, and CKD did not significantly impact post-infusion EF improvement ($p>0.05$). Despite 74% of the study population having DM and 76% having HTN, no statistically significant association was found between these conditions and EF response. This suggests that levosimendan's beneficial effects on cardiac contractility may be independent of comorbid disease states, aligning with findings from previous HF registries but contrast with data from the Casino [13] and Survive trials [14].

This study demonstrates that a 24-hour levosimendan infusion significantly improves EF in HFrEF patients but may lead to renal impairment without major electrolyte disturbances. The results align with major clinical trials, reinforcing levosimendan's efficacy as an inotropic agent while highlighting the need for cautious use in patients with renal dysfunction.

Conclusion

- This study demonstrates short-term EF improvement with levosimendan in acute decompensated HFrEF patients. The EF improvement aligns with LIDO, RUSSLAN, and CASINO trials, confirming levosimendan's superior inotropic effects over traditional agents.
- However, it also highlights potential renal function decline, necessitating careful patient selection and monitoring. The renal dysfunction findings support REVIVE II and LEVO-CTS.
- This study found no major electrolyte imbalances, suggesting a relatively stable profile in this patient cohort.
- In conclusion, levosimendan is a promising inotropic therapy for HFrEF, especially in patients, but its renal impact requires further investigation before widespread adoption in high-risk patients.

Limitations of the study:

- The study was a hospital-based study, and as such findings may not be a true representative of what is obtained in the general population.
- Key hemodynamic parameters such as cardiac output, PCWP, cardiac index or systemic vascular resistance were not evaluated.
- The lack of a control group with an alternate inotrope makes it difficult to say that levosimendan is superior.
- The exact mechanism of renal dysfunction needs further exploration.

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Conflicts of interest: There are no conflicts of interest.

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