



Outcomes of the patients of heart failure with reduced ejection fraction receiving inotropic support in initial 6 hours: Insights from Manipal Heart Failure Registry

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ABSTRACT

Heart failure (HF) is responsible for 1.8 million admissions annually in India with an additional burden of mortality and re-hospitalizations. Positive inotropes with multiple mechanisms, such as dopamine and levosimendan, are being used for more than three decades to treat the patients of acute HF with reduced ejection fraction (HFrEF). This study compared the outcomes of the dopamine and the levosimendan up to 180 days. We have selected the patients from Manipal Heart Failure Registry who were diagnosed to have HFrEF (left ventricular EF less than 50%) and were initiated on either dopamine or levosimendan in first 6 hours of hospitalization. The study included a total of 187 patients; among them, 120 patients were analyzed in the dopamine group, and 67 patients in the levosimendan group. Dopamine was initiated as intravenous infusion with the dose of 2.5 microgram/kilogram/minute (mcg/kg/minute) and up-titrated up to 10 mcg/kg/minute. Levosimendan was also administered intravenously with a dose of 0.1 mcg/kg/minute and up-titrated up to 0.4 mcg/kg/minute. The primary outcomes include a composite of all-cause mortality and re-hospitalization at 30-days and 180-days follow-ups. The in-hospital mortality, 30-days mortality and 180-days mortality, and composite outcomes were noted higher in levosimendan treated patients even after matched demographic parameters (age and gender) and comparable comorbidities and risk factors, i.e., smoking, alcohol consumption, hypertension, diabetes mellitus, and atrial fibrillation. However, reduced EF, raised serum creatinine, procalcitonin, and N-terminal pro b-type natriuretic peptide levels and high use of digoxin were noticed in levosimendan group during the initial period of index-hospitalization and these can be considered as confounding factors for future studies.

INTRODUCTION

About 38 million individuals are living with Heart failure (HF) worldwide. HF is responsible for 1.8 million admissions annually in India with a huge burden of mortality and re-hospitalizations (Braunwald, 2015). HF is a clinical array of alterations in the heart structure or/and function (diastolic or systolic) which declines the desired circulatory functions

(Ponikowski *et al.*, 2016). The hemodynamic models showed that the HF is a defect in cardiac contractility. The drugs named inotropes that alter the cardiac contractility have been considered as an attractive pharmaco-therapeutic target (Felker and O'connor, 2001). Positive inotropes are being used for more than three decades to treat the patients of acute HF with reduced ejection fraction (HFrEF) (Tariq and Aronow, 2015). Clinical presentation of acute HF includes the new onset or sudden deterioration of signs and symptoms which extends from worsening dyspnea to pulmonary edema or acute critical stage of cardiogenic shock. Beta-adrenergic agonists, calcium-sensitizer, and phosphodiesterase III inhibitors are three classes of inotropes currently trending in practice with distinct mechanisms (Bistola and Chioncel, 2017). Dopamine

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and levosimendan are two important inotropes that show mixed mechanisms being used in acute decompensated HF (ADHF) or refractory HF for immediate relief from symptoms. Dopamine causes vasodilation at low dose administration by stimulating β -receptors and α -receptors which independently enhance the cardiac output and improve symptoms. Levosimendan improves myocardial contractility and hemodynamics by sensitizing troponin C to calcium; it shows anti-ischemic and vasodilatory effects too (Guha *et al.*, 2018). These drugs are associated with short-term recovery from symptoms but did not show any long-term survival benefits (Felker and O'Connor, 2001). Data on the comparison of the outcomes related to both drugs in acute HFrEF patients are very limited and not demonstrated clearly. Hence, this study was designed to compare the composite outcomes, including mortality and re-hospitalizations up to 180 days from the index hospitalization.

MATERIALS AND METHODS

Study design and site

The Manipal Heart Failure Registry (MHFR) is a prospective registry that documents the routine medical care and pattern of therapeutic management and long-term HF-related outcomes, including mortality and re-hospitalizations. The study was conducted at a South Indian tertiary care hospital.

Study population/inclusion

The study included the patients admitted to intensive care settings of the hospital for HF management between January 2016 and December 2016. We have selected the patients from MHFR who were diagnosed to have HFrEF (left ventricular ejection fraction less than 50%) and initiated on either dopamine or levosimendan in first 6 hours of hospitalization. The study divided them into two groups based on the inotropic support (dopamine or levosimendan) they received initially.

Treatment details

Dopamine or levosimendan was given initially to manage the patients with worsened symptoms at index-hospitalization. Dopamine was initiated as an intravenous (IV) infusion with a dose of 2.5 microgram/kilogram/minute (mcg/kg/minute) and up-titrated up to 10 mcg/kg/minute. Levosimendan was also administered as an IV infusion with a dose of 0.1 mcg/kg/minute and up-titrated up to 0.4 mcg/kg/minute. Both the drugs were used for a minimum of 12 hours.

Study outcomes

The primary outcome studied was a composite of all-cause mortality and re-hospitalization. We have documented in-hospital mortality, 30-days cumulative mortality, and 180-days cumulative mortality along with re-hospitalizations within 180 days. Composite outcomes/events were including all-cause mortality and re-hospitalizations at 30-days and 180-days follow-ups. Re-hospitalization or mortality, whichever appeared first was taken to calculate the duration of events during follow-ups. Composite events are not the exact sum of mortality and re-hospitalizations.

Parameters observed

Socio-demographic details, including gender, age, and clinical characteristics, including etiology, details of cardiac and non-cardiac comorbid conditions were documented. New York Heart Association (NYHA), functional classes, signs, and symptoms at presentation, were recorded. Investigations, including biomarkers, ejection fraction by an echocardiogram (ECHO), and further lab tests to diagnose co-morbidities were documented. Duration of hospitalization and intensive care unit stay was computed to correlate the outcomes in both the groups. Details about inotropic drugs, i.e., types, dose, and duration of therapy along with other concurrent drugs were noted and analyzed. In-hospital and post-discharge events were also recorded up to 180 days after index-hospitalization.

Ethical considerations

The institutional ethical committee has approved the study with the ethical approval number MUEC/20/2015-16. Informed consent was signed by all eligible patients recruited for the study.

Statistical analysis

Means and the standard deviation were used to present continuous data. Proportions were calculated for categorical data. Categorical variables were compared using the Chi-square test, and continuous variables were compared through *t*-tests. Thirty days-mortality and 180-days mortality were estimated as cumulative proportions. Univariate survival analysis was performed to compare the prognosis between dopamine and levosimendan using Kaplan–Meier survival plots and log-rank test. Assumption of deviation from the proportional hazard was analyzed through log-minus-log plots. Statistical significance was considered at *p* value less than 0.05. IBM SPSS Statistics version 20.0 (IBM Corp. Armonk, NY) was used for data entry and statistical analysis purpose.

RESULTS

Socio-demographic and clinical characters

We, therefore, included a total of 187 patients of HFrEF who received either dopamine or levosimendan during the mentioned period. Among the total, 120 patients were analyzed in the dopamine group and 67 patients in the levosimendan group. Socio-demographic parameters including age, gender, and social habits were assessed which were not different significantly ($p > 0.05$) in both the groups. Ischemic heart disease was presented in 64% of patients in the dopamine group against 31.5% in the levosimendan group, and it was significantly high ($p < 0.001$).

Comorbid conditions, NYHA functional class, signs, and symptoms were noted at first presentation during index hospitalization (Table 1). Hypertension was presented in the highest proportion of patients (46.5%) followed by diabetes mellitus (39.0%) and atrial fibrillation (AF; 20.9%), and distribution of comorbidities was not significantly different in both the study groups ($p > 0.05$). Use of ventilation (mechanical or non-invasive) and length of stay (LOS) in the hospital were assessed under health resources utilization (HRU), and there was no significant difference noted in the utilization of healthcare

Table 1. Socio-demographic and clinical characters of the study population and comparison between dopamine and levosimendan groups.

Variables	Total [n, 187 (%)]	Dopamine Group [n, 120 (%)]	Levosimendan group [n, 67 (%)]	p value
Socio-demographic details				
Age, mean \pm SD, median (years)	64.6 \pm 13.7, 67	64.7 \pm 13.9, 68	64.5 \pm 13.6, 65	0.928
Male gender	121 (64.7)	72 (60.0)	49 (73.1)	0.072
Smoking	86 (45.9)	55 (45.8)	31 (46.3)	0.952
Alcohol	97 (51.9)	61 (50.8)	36 (53.7)	0.092
Ischemic etiology	98 (52.4)	77 (64)	21 (31.5)	<0.001
Comorbidities				
Hypertension	87 (46.5)	55 (45.8)	32 (47.7)	0.429
Diabetes mellitus	73 (39.0)	42 (35.0)	31 (46.2)	0.252
Atrial fibrillation	39 (20.9)	23 (19.2)	16 (23.9)	0.399
Renal disease	39 (20.8)	21 (17.5)	18 (26.8)	0.057
Thyroid dysfunction	19 (10.2)	13 (10.8)	6 (8.9)	0.890
New York Heart Association functional class, sign and symptoms at index-hospitalization				
NYHA III/IV	144 (77.0)	93 (77.5)	51 (76.4)	0.067
Pulmonary rales	152 (81.3)	96 (80.0)	56 (83.6)	0.742
Low urine output	94 (50.3)	46 (38.3)	48 (71.6)	0.004
Congestion in chest X-ray	126 (67.4)	67 (59.8)	59 (88.1)	<0.001
Healthcare resources utilization				
Ventilation (NIV/MV)	89 (47.6)	102 (85.0)	53 (79.1)	0.128
Length of stay (days)	6.4 \pm 4.8	6.7 \pm 4.5	5.8 \pm 5.3	0.229
Investigations (Mean \pm SD and/or median if applicable)				
Ejection fraction (%)	36.3 \pm 9.3	37.9 \pm 7.9	33.4 \pm 7.7	<0.001
Systolic BP (mmHg)	108.1 \pm 22.8	101.5 \pm 16.8	119.9 \pm 26.2	0.093
Heart rate (per min.)	89.7 \pm 19.1	92.1 \pm 21.4	84.1 \pm 10.3	0.023
NT-proBNP (median) (pg/ml)	9,154 \pm 8,283, 4,702	6,979.8 \pm 5,602, 3,749	13,140 \pm 11,748, 8,455	<0.001
Hemoglobin (g/dl)	12.2 \pm 2.2	12.5 \pm 2.3	11.8 \pm 2.1	0.062
Total leucocyte count (*10 ³ /microL)	12.2 \pm 5.2	12.5 \pm 5.2	11.4 \pm 9	0.163
Serum Creatinine (mg/dl)	1.1 \pm 0.6	0.9 \pm 0.5	1.4 \pm 0.8	0.032
Glycosylated hemoglobin (%)	6.7 \pm 1.7	6.7 \pm 1.9	6.7 \pm 1.2	0.989
Albumin (g/dl)	3.7 \pm 0.6	3.8 \pm 0.6	3.6 \pm 0.7	0.048
Procalcitonin (ng/ml)	2.5 \pm 1.3	1.8 \pm 1.2	3.7 \pm 2.1	0.001

SD = Standard deviation, NIV = Non-invasive ventilation, MV = Mechanical ventilation, NT-proBNP = N-terminal pro b-type natriuretic peptide.

resources between dopamine and levosimendan group (P, 0.128 and 0.229 respectively). Details of the investigations done during the index-hospitalization are given in Table 1. High N-terminal pro b-type natriuretic peptide (NT-proBNP) (13,140 \pm 11,748 pg/ml vs. 6,979 \pm 5,602 pg/ml; $p < 0.001$) and serum creatinine (1.4 \pm 0.8 mg/dl vs. 0.9 \pm 0.5 mg/dl; $p = 0.032$) levels and low EF (33.4 \pm 7.7% vs. 37.7 \pm 7.9%; $p < 0.001$) were recorded during first 6 hours of the index-hospitalization in levosimendan group, all the parameters were significantly different from the patients who received dopamine.

Concurrent medications

The median duration of dopamine use was 19 hours (range 12–50 hours), whereas levosimendan was used for 23 hours (range 12–72 hours). Medications other than dopamine and levosimendan were used for symptoms relief and the management of the comorbidities. Evidence-based drugs, i.e., IV furosemide were administered in 93.3% and 92.5% patients in the dopamine

group and levosimendan group, respectively with no significant difference. The dose of IV furosemide was significantly low in the dopamine group than the comparison (levosimendan) group (p value, 0.015). Disease-modifying drugs and guidelines directed medical therapy (GDMT), such as beta-blockers (BB), angiotensin-converting-enzyme inhibitor (ACE-Is), angiotensin II receptor blockers (ARBs), and aldosterone antagonists were given in similar proportions in both the groups ($p > 0.05$). Drugs including antiplatelet agents, statins, amiodarone, oral hypoglycemic agents (OHAs), and insulin were used to manage comorbid conditions and details are presented in Table 2. Digoxin was used in a very high proportion in addition to levosimendan than dopamine (61.2% vs. 10.8%; $p < 0.001$).

Outcomes

Composite outcomes and cumulative mortality for 180-days follow-up period were calculated for all the patients and between both the study groups. There was a significant difference

noted in all types of outcomes except re-hospitalizations alone, between dopamine group and levosimendan group (Table 3).

Prognosis comparison

Survival analysis using Kaplan–Meier curve was performed for in-hospital mortality, 30-days composite outcomes, 180-days cumulative mortality, and 180-days composite outcomes between dopamine and levosimendan groups. Patients in the dopamine group showed significantly prolonged survival than the levosimendan group in all outcome parameters by log-rank testing (Fig. 1).

DISCUSSION

Acute HF patients appear critical due to several other conditions, such as ischemia, left ventricular dysfunction, inflammatory activation, and arrhythmias. Blood pressure (BP) and heart rate (HR) control and management of acute coronary syndromes and arrhythmias in HF patients are the primary goals (Huang *et al.*, 2013). When HF is acute and severe and not responding to first-line drugs, inotropes are usually given to stabilize the hemodynamics (Bayram *et al.*, 2005). Outcomes were compared for 180 days between dopamine and levosimendan in acute HF patients with reduced ejection fraction. The study showed better outcomes and survival in the dopamine group while considering equally distributed baseline characteristics, i.e., socio-demographic parameters, comorbidities, NYHA functional class at presentation and HRU and concurrent drugs with no significant difference except for digoxin. High NT-proBNP, serum creatinine, procalcitonin levels, and low EF, and ischemic etiology in levosimendan group and use of digoxin in addition to levosimendan in initial period of hospitalization were noticed as confounding factors or the factors influencing the poor outcomes in levosimendan group in comparison to dopamine group.

Inotropes are not included in GDMT or evidence-based therapy for heart failure treatment, but they are being used worldwide despite the sobering results of clinical trials. This is may be due to limited therapeutic options for the sub-groups of advanced HF where BB, ACE-Is, or diuretics fails to improve

symptoms or the patients need inotropes as additional support (Felker and O'connor, 2001). Long-term inotropic therapy is not recommended as long-term outcomes are not in favor, but it can be used for long-term as a bridging therapy in the patients waiting for definitive treatment (Upadya *et al.*, 2004). Achieving adequate diuresis, regressing the symptoms of congestion, limiting the frequent hospitalizations, as well as LOS, are other appropriate goals of therapy in acute HF patients.

The current study presents the significant difference in EF between both the groups, which showed that the patients in levosimendan group were having severe left ventricle dysfunction as compared to the dopamine group which may have an impact on the long-term outcomes. An almost similar distribution of functional class in both groups gives additional strengths to the results. The high proportion of low-urine output and significantly high serum creatinine in patients who received levosimendan showed the choice of levosimendan over dopamine in renal injury patients. Use of dopamine is always controversial due to its dose-dependent adverse renal effect. Low-dose dopamine (LDD) (<3 mcg/kg/minute) shows dopaminergic effect by activating dopaminergic receptors resulting in vasodilation of coronary and renal arteries. Intermediate dose (3 to 10 mcg/kg/minute) of dopamine increases the inotropy and HR by activating beta-adrenergic receptors, but high dose (>10 mcg/kg/minute) acts on alfa-adrenergic receptors as an agonist and causes peripheral vasoconstriction (Francis *et al.*, 2014). Initially, LDD was recognized as “renal dose” but it remained controversial after Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE AHF) trial. ROSE AHF concluded that the LDD was not beneficial for renal care in acute HF patients (Chen *et al.*, 2013). A meta-analysis concluded that the LDD decreases the serum creatinine levels and promotes diuresis in HF patients. LDD enhances the estimated glomerular filtration rate (Xing *et al.*, 2016). The Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) randomized trial studied 161 patients ADHF in three different groups of high-dose furosemide, low-dose furosemide with LDD and low-dose diuretics. LDD showed no benefits in short-term and long-term mortality and other secondary outcomes (Triposkiadis *et al.*, 2014). In the present study the low-dose of furosemide was used with low or intermediate

Table 2. Concurrent medications during index-hospitalization.

Drugs	Total [n, 187 (%)]	Dopamine group [n, 120 (%)]	Levosimendan group	p value
IV furosemide	174 (94.1)	112 (93.3)	62 (92.5)	0.503
Dose of furosemide (mean ± SD)	39.7 ± 20.1	36.9 ± 19.1	46.1 ± 21.1	0.015
Spironolactone	62 (33.2)	38 (31.7)	24 (35.8)	0.192
Isosorbide dinitrate/hydralazine	92 (49.4)	63 (52.5)	29 (43.2)	0.159
Antiplatelet drugs	166 (88.8)	107 (89.2)	59 (88.1)	0.862
Statin therapy	163 (87.2)	106 (88.3)	57 (85.1)	0.258
Beta blockers	67 (35.8)	44 (36.7)	23 (34.3)	0.672
CCBs	34 (18.2)	21 (17.1)	13 (19.4)	0.512
ARBs/ACE-Is	97 (51.9)	66 (55.0)	32 (47.8)	0.232
Amiodarone	29 (15.5)	20 (16.7)	9 (13.4)	0.548
Digoxin	54 (28.9)	13 (10.8)	41 (61.2)	<0.001
OHAs	49 (26.2)	31 (25.8)	18 (26.9)	0.638
Insulin	68 (36.4)	43 (35.8)	25 (37.3)	0.616

CCBs = Calcium channel blocker, ACE-I = Angiotensin-converting-enzyme inhibitor, ARB = Angiotensin II receptor blockers, OHA = Oral hypoglycemic agent.

dose (<10 mcg/kg/minute) of dopamine and it showed the significantly better short-term and long-term outcomes. DAD-HF analyzed 60 patients showed that the LDD with low-dose furosemide did not show any improvement in renal injury in ADHF patients (Giamouzis *et al.*, 2010). In the present study, renal parameters were not analyzed to compare the effect of LDD in HF patients with renal injury.

There is no head-to-head comparison available for the efficacy and long-term outcomes between dopamine and levosimendan where comparisons of dopamine with dobutamine and levosimendan with dobutamine are well studied. Dzhaiani *et al.* (2011) have compared the short-term efficacy of levosimendan and dopamine in 30 patients with resistant cardiac failure in Russia

Table 3. 180-days outcomes and prognosis in the study population.

Outcomes	Total [n, 187 (%)]	Dopamine group [n, 120 (%)]	Levosimendan group [n, 67 (%)]	p value
Mortality				
In-hospital	39 (20.8)	17 (14.2)	22 (32.68)	0.001
30-days mortality	46 (24.6)	21 (17.5)	25 (37.3)	0.001
180-days	60 (32.1)	30 (25.0)	30 (44.7)	0.002
Re-hospitalization within 180-days				
1 or >1	27 (31.6)	15 (26.7)	12 (40.3)	0.315
Composite events (mortality and re-hospitalizations)				
30-days	61 (32.6)	29 (24.2)	32 (47.8)	<0.001
180-days	84 (44.4)	43 (35.8)	41 (59.7)	<0.001

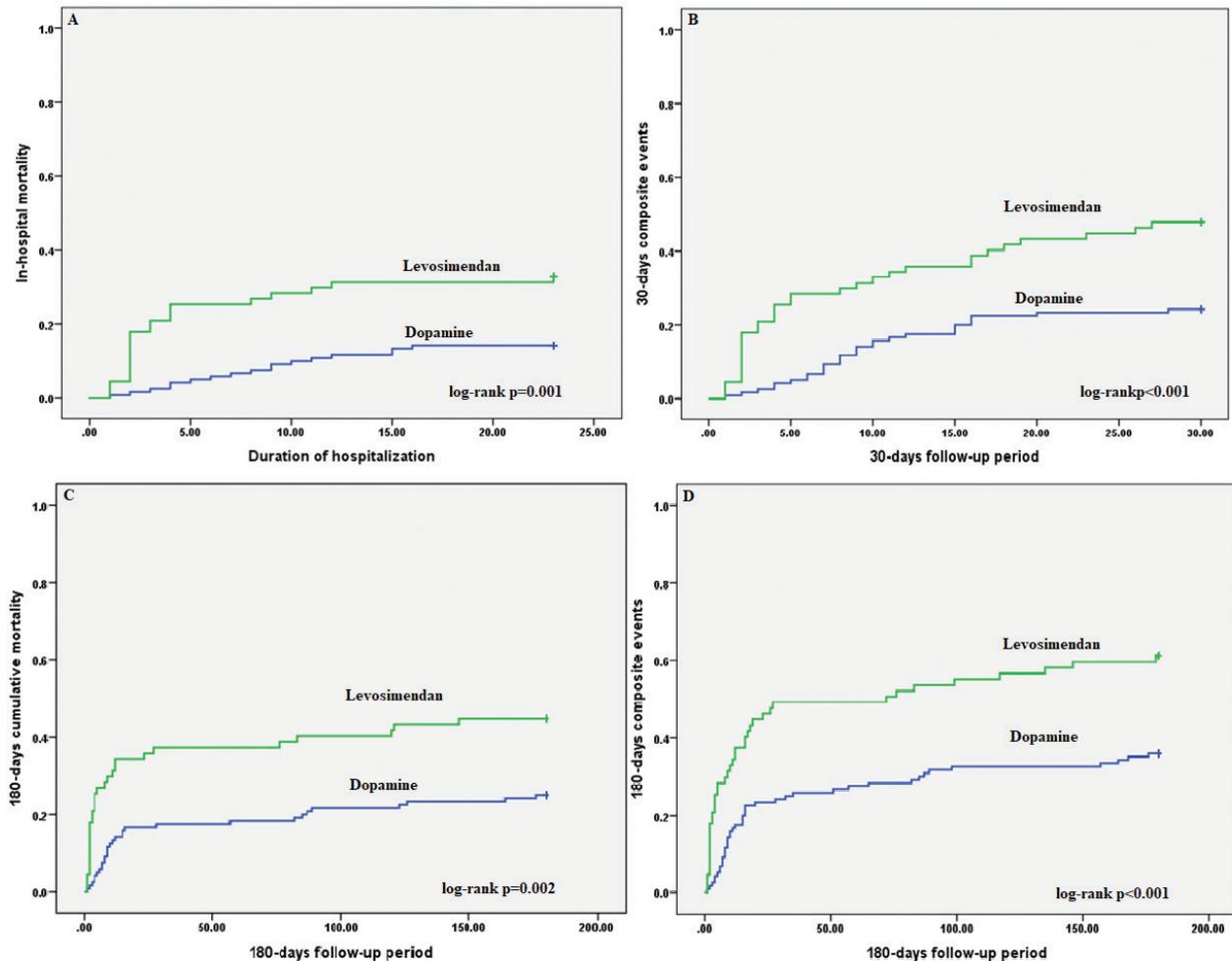


Figure 1. Mortality and composite outcomes/events at various follow-ups in dopamine and levosimendan groups. Kaplan–Meier mortality/composite events curves based on inotropic treatment in initial 6-hours at index-hospitalization. (A) Initial inotropic therapy and in-hospital mortality; (B) initial inotropic therapy and 30-days composite events; (C) initial inotropic therapy and 180-days cumulative mortality; and (D) initial inotropic therapy and 180-days composite events.

and concluded that the levosimendan shows better prognosis than dopamine by producing earlier regress of symptoms and increased cardiac contractility.

Levosimendan is being used in several indications including severe LV dysfunction patients all around the globe except United States (De Luca *et al.*, 2006; Gustafsson *et al.*, 2017; Tavares *et al.*, 2018). Levosimendan is used in 1/3 of the study population and not shown any positive results, and supported by various studies (Mathieu and Craig, 2011). Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) a randomized controlled trial comparing levosimendan with dobutamine involving 1,327 patients concluded that the levosimendan did not reduce the 180-days all-cause mortality. Despite decreasing NT-proBNP levosimendan did not affect any secondary outcomes including re-hospitalizations (Mebazaa *et al.*, 2007). Randomised Evaluations of Intravenous Levosimendan Efficacy (REVIVE II) also did not show the satisfactory benefits in long-term outcomes although the study was conducted to describe short-term outcomes of levosimendan (Packer *et al.*, 2013). A meta-analysis comparing levosimendan and dobutamine in critically ill acute HF patients concluded that the levosimendan shows significant better improvements in the patients undergoing cardiac-surgery, receiving BB therapy and/or presented with ischemic etiology (Huang *et al.*, 2013). A Greek study supported the prolonged infusion of levosimendan and its association with improved neuro-hormonal and clinical response (Aidonidis *et al.*, 2011) and it also showed improved myocardial contractility in percutaneous coronary intervention-treated ST-elevation myocardial infarction patients who developed acute HF (Husebye *et al.*, 2013). The recent randomized trials LION-HEART (Intermittent Intravenous Levosimendan in Ambulatory Advanced Chronic Heart Failure Patients) and LevoRep (Pulsed Infusions of Levosimendan in Outpatients with Advanced Heart Failure) showed the mixed opinion about levosimendan efficacy and safety in acute HF patients (Altenberger *et al.*, 2014; Comin-Colet *et al.*, 2018)

This is purely an observational study comparing the long-term outcomes between the patients receiving levosimendan or dopamine in initial 6 hours of hospitalizations, which showed lower in-hospital mortality, improved outcomes at 30 days and 180 days in dopamine group. Some more randomized head-to-head clinical trials are recommended to understand the mechanism and to confirm the results of this observational study. Further studies can be performed keeping the baseline EF similar for the study groups.

CONCLUSION

In patients who are age and gender-matched with comparable comorbidities and risk factors, i.e., smoking, alcohol consumption, hypertension, diabetes mellitus, and AF, levosimendan group had higher in-hospital mortality, 30-days mortality and 180-days mortality, and composite outcomes. However, the levosimendan group also had reduced ejection fraction, raised serum creatinine, procalcitonin, and NT-proBNP levels and very high use of digoxin in initial period of index-hospitalization and these can be considered as confounding factors for future studies.

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AUTHOR'S CONTRIBUTION

All mentioned authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICT OF INTEREST

Dr. Tom Devasia has received the research grants from Novartis Pharma, India, but this has no impact on Manipal Heart Failure Registry. Dr. Ajit Singh and Dr. Ganesh Paramasivam are working as co-investigator in a clinical trial funded by Novartis Pharma, India but it does not affect the current study. Dr. Prasad N Shetty also works for Novartis funded clinical trial as sub-investigator, but it does not relate to current study. Other authors do not declare any conflict of interests.

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