



Comparative study of two inotropes levosimendan and dobutamine in critically ill patients suffering from heart failure

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ABSTRACT

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Objective: Acute heart failure frequently happens in critically ill patients due to myocardial injury, cardiac dysfunction, arrhythmias, and inflammatory mediators. Till now, the outcomes of studies comparing levosimendan with dobutamine for patients requiring inotropic support remain controversial and ambiguous. The present study was aimed to compare the effects of levosimendan and dobutamine in the management of critically ill patients in ICU and establish preference of one over the other drug.

Methodology: In this study 100 critically ill patients with clinical diagnosis of heart failure or impending heart failure due to any cause of age between 21 years to 80 years (left ventricular ejection fraction < 35%) in ICU were included and randomly divided into 2 groups; Group-1 (n=50) received inj levosimendan and Group-2 (n=50) which received inj dobutamine. The parameters recorded during study were: heart rate (beats/min), systolic blood pressure (mmHg), stroke volume (ml), cardiac output (l/min), cardiac index (l/min/m²), brain natriuretic peptide (pg/ml), requirement of inotropic agent and 7 day survival. Baseline parameters of the patient at "0" h was recorded, then the inotrope (levosimendan or dobutamine) was started. After this the parameters were recorded at 24 h, 48 h and 5th day of study and follow-up of patient was done upto 7 days. SPSS for Windows version 16.0 software was used for statistical analysis. For non-continuous data Chi-square test was used. The mean and standard deviation of the parameters compared using student "t" test. The p < 0.05 was considered as significant.

Results: The distribution of patients according to age, sex and body surface area was comparable (p > 0.05) in both the groups. Heart rate decreased significantly in both the groups at 24 h and 5th day, although it remained higher in Group-1 patients receiving levosimendan. Systolic blood pressure and Cardiac Index (CI) increased significantly in both the groups but was more in Group-1 patients receiving levosimendan at all times. Cardiac output increased significantly in Group-1 pts whereas in Group-2, after an initial increase for first 48 hrs ultimately decrease in cardiac output was observed on 5th day. 7 Day survival was more (56%) in Group-1 patients as compared to 52% in Group-2 patients.

Conclusion: Based upon the results of our study, we conclude that levosimendan shows better results than dobutamine in maintaining hemodynamic stability in critically ill patients. Larger, multi-center studies may have to be done for confirming or discrediting our results.

Key words: Critically ill; Heart Failure; Levosimendan; Dobutamine; Treatment outcome.

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INTRODUCTION

Acute heart failure (AHF) frequently happens in critically ill patients due to myocardial injury, cardiac dysfunction, arrhythmias, and inflammatory mediators. First of all, the underlying cardiac disease and precipitating factors should be managed. Clinicians need to treat acute coronary syndromes, arrhythmias, hypertension or severe infections as soon as possible. Secondly, vasodilators and/or diuretics are usually administered to improve symptoms. When AHF is severe and not responding to first line treatments above, inotropic agents may be used.¹ Positive inotropic agents are usually used to relieve the symptoms of tissue hypoperfusion and ensure the blood supply to vital organs. Thus, inotropes are suitable for low cardiac output syndrome (LCOS), and are particularly effective in patients with lower blood pressure, and intolerance or poor response to vasodilators and diuretics.² Inotropes are also used when patients with severe sepsis or septic shock present with cardiac dysfunction despite sufficient fluid resuscitation, according to the international guidelines for management of severe sepsis and septic shock.³ However, reliable data on comparing inotropic agents are still inadequate, and the challenge to clinicians in selection of proper inotropes has been emphasized in a few reports.^{4,6} As a new calcium sensitizer, levosimendan has inotropic and vasodilatory actions mediated by the sensitization of contractile proteins to calcium, the opening of potassium channels and inhibition of phosphodiesterase-3. It has been used in many developed countries and is recommended in the European Society of Cardiology guidelines for treatment of AHF.⁷ In fact, levosimendan is the first inotropic drug found to establish a positive effect on patient survival time for any inotropic drug in contrast with placebo. On the other hand Dobutamine has been the most common choice in the treatment of AHF in recent decades, with an expected effect on short-term improvement of symptoms. In clinical settings, it is still confusing to select between levosimendan and dobutamine for patients requiring inotropic support. Until now, outcomes of studies comparing levosimendan with dobutamine are controversial and ambiguous. We compared the effects of levosimendan and dobutamine in the management of critically ill patients in ICU to help establish preference of one over the other drug.

METHODOLOGY

This study was conducted in the Intensive Care Unit of Department of Anaesthesiology, Sir Sunderlal Hospital, Banaras Hindu University. The attendants of the participants of this study were explained of the procedure and informed consent was taken. It

was a prospective, open labelled and randomized study comparing the effects of levosimendan and dobutamine in the management of critically ill patients in ICU. In this study 100 patients from ICU were included and were randomly divided into 2 groups: Group-1 (n = 50) received infusion of levosimendan (12 $\mu\text{g}/\text{kg}$ over 10 min followed by 0.1 $\mu\text{g}/\text{kg}/\text{min}$ for 24 h) and Group-2 (n = 50) received infusion of dobutamine (5 to 10 $\mu\text{g}/\text{kg}/\text{min}$). Other vasopressors like noradrenaline/dopamine were added if patient remained hypotensive 30 min after starting therapy. The inclusion criteria were all patients with clinical diagnosis of heart failure or impending heart failure due to any cause of age between 21 y to 80 y, e.g. left ventricular ejection fraction < 35%; whereas exclusion criteria were significant aortic or mitral valvular lesion, restrictive or hypertrophic cardiomyopathy, sustained ventricular tachycardia or ventricular fibrillation, second or third degree atrioventricular block, severe renal failure (serum creatinine > 9 mg/dl), hepatic failure and pregnancy. The goals of therapy were; systolic blood pressure > 90 mmHg and cardiac index (CI) > 2.8 L/min/m². For invasive arterial BP monitoring an arterial cannula was introduced in radial or dorsalis pedis artery and connected to transducer. Other cardiac parameters e.g. stroke volume, cardiac output and cardiac index were derived from calculations obtained by transthoracic echocardiography using Sonosite® portable ultrasound machine with 5 Hz cardiac probe and various mathematical equations.

Brain natriuretic peptide (BNP) values were recorded in whole blood specimen with EDTA as anticoagulant, obtained by central venous catheter at the start of study, at 24 h, 48 h and on 5th day of starting the study. Baseline parameters of the patient at “0” h was recorded then the inotrope (levosimendan or dobutamine) was started at their respective doses as stated before. Follow-up of patient was done upto 7 days. The dose of levosimendan was kept constant throughout the study, whereas dose of dobutamine ranged from 5 to 10 $\mu\text{g}/\text{kg}/\text{min}$, although a vasopressor (noradrenaline/dopamine) was started during the study in cases where goals were not achieved by single drug. The following parameters recorded during study: heart rate (beats/min), systolic blood pressure (mmHg), stroke volume (ml), cardiac output (l/min), cardiac index (l/min/m²), brain natriuretic peptide (pg/ml), requirement of vasopressor (yes/no), 7 –day survival (yes/no).

The statistical analysis was done using SPSS for Windows version 16.0 software. For non-continuous data Chi-square test was used. The mean and standard deviation of the parameters studied during observation period were calculated for two treatment groups and compared using student “t” test. The critical value of “p” indicating the probability of significant differences was taken as <0.05 for comparisons.

RESULTS

The distribution of patients according to age, sex and body surface area was comparable ($p > 0.05$) in both the groups (Table 1, 2). Table 3 shows, HR decreased significantly in both the groups at 24 h and 5th day, although it remained higher in Group-1 patients receiving levosimendan. BP and CI increased significantly in both the groups but was more in Group-1 patients receiving levosimendan at all times. CO increased significantly in Group-1, whereas in Group-2, after an initial increase in CO for first 48 h ultimately decreased CO was observed on 5th day. SV increased significantly in both the groups, but was more in Group-2 patients receiving dobutamine. Brain natriuretic peptide (BNP) values decreased in both the groups with treatment although the difference was not statistically significant between the two groups. Noradrenaline was required initially in almost all patients in both the groups (Table 4). 7-day survival was more (56%) in Group-1 as compared to 52% in Group-2 patients (Table 5).

DISCUSSION

For the past 20 years, a large number of studies have shown that many inotropic agents increased mortality in critically ill patients requiring inotropic support. In treating critically ill patients with HF, especially during an emergency, inotropes are needed. Clinical trials and reviews of inotropes are needed to evaluate the efficacy of various inotropic agents and find out which is most suitable for this particular set of patients.

Dobutamine is a typical cyclic adenosine monop-hosphate (cAMP)-dependent inotropic agent, which is widely applied in clinical practice. As a new calcium-sensitizing positive inotropic agent, levosimendan is similar to dobutamine with regards to hemodynamic effects in patients requiring inotropic support. Whether or not levosimendan is better than traditional inotropes such as dobutamine is still controversial. Indeed, the similarity between the conventional inotropes and

Table 1: Comparative age, height, weight & body surface area

Variable	Group-2	Group-1	t-value	p-value
Age	35.00 ± 6.08	36.72 ± 4.98	-1.547	0.125
Height	154.88 ± 6.91	155.12 ± 4.71	0.202	0.839
Weight	57.88 ± 5.25	58.84 ± 4.37	0.993	0.322
BSA	1.4628 ± 0.08	1.4880 ± 0.02	-2.052	0.043

Data given as Mean ± SD

Table 2: Comparative gender distribution

Sex	Group-1		Group-2	
	No.	%	No.	%
Male	34	68	32	64
Female	16	32	18	36
Total	50	100	50	100

$\chi^2=0.178; p=0.673$

Table 3 : Comparative hemodynamic and cardiac parameters at different times

Variables	Group-1 (Mean ± SD)	Group-2 (Mean ± SD)	t-value	p-value	
HR	0 h	105.72 ± 5.81	107.12 ± 7.44	-1.048	0.297
	24 h	103.47 ± 5.47	94.76 ± 5.20	11.452	<0.001
	48 h	101.27 ± 6.07	84.76 ± 6.20	13.000	<0.001
	5 Days	92.00 ± 3.70	67.31 ± 4.86	23.276	<0.001
IBPS	0 h	87.00 ± 3.71	86.42 ± 2.87	0.867	0.388
	24 h	103.62 ± 6.27	100.58 ± 2.91	3.045	0.003
	48 h	119.12 ± 5.08	101.29 ± 3.54	16.775	<0.001
	5 Days	128.214 ± 4.491	103.071 ± 2.478	25.934	<0.001
CO	0 h	4.356 ± 0.44	4.176 ± 0.25	2.493	0.014
	24 h	4.416 ± 0.32	5.054 ± 0.30	-16.508	<0.001
	48 h	4.853 ± 0.42	5.181 ± 0.38	-13.294	<0.001
	5 Days	4.950 ± 0.14	3.857 ± 0.12	5.473	<0.001
CI	0 h	2.544 ± 0.21	2.744 ± 0.37	1.657	0.101
	24 h	2.608 ± 0.18	2.129 ± 0.30	-8.069	<0.001
	48 h	2.706 ± 0.20	2.134 ± 0.33	-8.822	<0.001
	5 Days	2.714 ± 0.21	2.211 ± 0.32	-7.762	<0.001
SV	0 h	64.56 ± 5.19	66.36 ± 6.59	-1.516	0.133
	24 h	59.33 ± 5.08	62.92 ± 9.24	-4.322	<0.001
	48 h	61.18 ± 3.88	63.33 ± 5.78	-6.693	<0.001
	5 Days	62.50 ± 2.48	64.92 ± 4.20	-9.038	<0.001

HR-heart rate -Beats/min, IBPS-invasive blood pressure (systolic) mmHg, CO-cardiac output - L/min, CI-cardiac index - L/min /m² & SV-stroke volume-ml.

Table 4: Brain natriuretic peptide (BNP) values-pg/ml & use of vasopressors

Variables	Group-1 (Mean ± SD)	Group-2 (Mean ± SD)	t-value	p-value
BNP 0 h	550.16 ± 248.48	554.04 ± 200.12	-0.086	0.932
BNP 24 h	494.38 ± 237.35	531.29 ± 238.71	-.760	0.449
BNP 48 h	368.35 ± 228.11	344.00 ± 164.47	0.484	0.630
BNP 5Days	229.29 ± 42.71	233.85 ± 71.63	-.287	0.776
VASO 0 h	1.00 ± 0.00	1.00 ± 0.00	-	-
VASO 24 h	1.25 ± 0.43	1.25 ± 0.43	0.000	1.000
VASO 48 h	1.65 ± 0.48	1.56 ± 0.50	0.695	0.490
VASO 5Days	2.00 ± 0.00	2.00 ± 0.00	-	

Table 5: Seven-day survival

7 D Survival	Group-1		Group-2	
	No.	%	No	%
Survival	28	56	26	52
Mortality	22	44	24	48
Total	50	100	50	100

$$\chi^2=0.161; p=0.688$$

levosimendan has been demonstrated in two large clinical trials: SURVIVE (Mebazaa *et al.*, 2007)⁸ and REVIVE II (Cleland *et al.*, 2006)⁹. No survival benefit was found in the largest RCTs, which compared levosimendan with dobutamine in patients with acute decompensated HF.⁸

In recent years, several meta-analyses have been published and majority of which have favorable results for levosimendan,¹⁰⁻¹⁴ despite one negative conclusion.¹⁵ Among the studies with favorable results, there are three studies merely comparing levosimendan with conventional inotropes and placebo adopted in the control group but without further comparing it with dobutamine.¹¹⁻¹³ The other two studies have compared levosimendan with dobutamine; however, the result have been inconsistent. In all three meta-analyses on mortality of levosimendan vs. dobutamine, only one was in favor of levosimendan,¹⁰ two of them were negative.¹⁴ Recently, a few new outcomes of clinical trials on levosimendan vs. dobutamine have been released.

A few studies on levosimendan vs. dobutamine included in meta-analyses¹⁰⁻¹⁴ found survival benefits in patients after coronary revascularization, but a negative result when levosimendan was compared with dobutamine. This result in cardiac surgery is certainly worthy of clinicians' attention, where inotropic drugs are often required for postoperative low cardiac output syndrome.

A β -adrenergic agonist (dobutamine) is frequently administered under this circumstance; although it usually shows a beneficial hemodynamic effect, but it may cause myocardial ischemia and arrhythmias. Levosimendan may favor the recovery of myocardial dysfunction after cardiac surgery for its anti-ischemic, cardio-protective and vasodilatory effects. The reason for the survival benefit in subpopulation of cardiac surgery in our analysis is worth discussing. Firstly, acute myocardial ischemia and ischemia-reperfusion may be the main mechanism for LCOS after cardiac surgery with extracorporeal circulation (ECC). Meanwhile, four out of five trials in cardiac surgery included patients with ischemic heart disease (IHD) and undergoing CABG. Two of them included patients who all were with IHD and underwent CABG. It implied that levosimendan may be more effective in improving myocardial ischemia and restoring myocardial function in contrast with dobutamine. Myocardial dysfunction in cardiac surgery may be more likely to recover than that in patients with acutely decompensated congestive heart failure (ADCHF) or chronic HF in cardiology setting. The sub analyses in the subgroup including ischemic HF (IHF) patients and in the subgroup in which all patients had IHF, both indicated a favorable result to levosimendan. In fact, 15 out of 19 trials on mortality are totally or partly concerning patients with IHF, who account for more than half of the study population. It's an encouraging finding about IHF, because with the development of global economy and improvement of living standards, there are increasing number of patients with coronary heart disease and IHF around the world and especially in developing countries.

Bayramet *al.*¹ reported that post-discharge mortality was increased for short-term use of classical inotropes, particularly in patients with IHD. Levosimendan may be superior to dobutamine in patients with IHF as shown by the results of many pharmacological studies and animal studies. Levosimendan demonstrates positive inotropic properties without increasing myocardial oxygen consumption¹⁶ and impairing ventricular relaxation¹⁷ in failing hearts; on the other hand, it has a vasodilatory effect mediated by activation of adenosine triphosphate (ATP)-sensitive potassium channels, which reduces cardiac preload and afterload.^{8,16} In addition, levosimendan can increase the diastolic coronary flow velocity through an ATP-sensitive potassium channel opening effect on coronary vasculature.¹⁹

In contrast, one of the dobutamine's fatal weaknesses is increasing myocardial oxygen demand and further causing myocardial injury. Therefore, dobutamine can worsen myocardial ischemia in patients with ischemic cardiomyopathy, especially in the setting of acute myocardial ischemia.²⁰ In patients with acute myocardial infarction (AMI) complicated by

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cardiogenic shock secondary to severe left-ventricular systolic dysfunction requiring inotropic support, levosimendan increased both CI and left ventricular ejection fraction more significantly than dobutamine.

However, most of studies in our analysis did not include patients with AMI. In the SURVIVE study, which included patients with AMI, no survival benefit was found in the subpopulation of AMI. Another study including patients with AMI concluded that levosimendan did not improve long-term survival in STEMI patients revascularized by PCI who developed cardiogenic shock when compared to dobutamine.²¹ Thus, there is still no convincing evidence demonstrating that levosimendan can improve the prognosis of patients with AMI when compared with dobutamine.

Disappointingly, the research result of subgroups in a cardiology setting was not satisfactory. On one side, it may indicate levosimendan is not better than dobutamine in all kinds of patients with HF and the efficacy of levosimendan in a cardiology setting may be incomparable to those in cardiac surgery. On the other side, it may relate to removing the CASINO study (Zairiset *al.*, 2004)²², which had a lot of problems in study quality. The CASINO study was criticized for performing analyses only on patient-on-treatment instead of intention-to-treat principle.

Many experts argued if the drop-outs in that study were to be included, the magnitude of the effect might be minimal to negligent. However, most of previous meta-analyses about levosimendan included the CASINO study.^{10,13,15} With the inclusion of the CASINO study, the result of analysis in cardiology setting would be in favor of levosimendan (237 of 1142 [20.8%] in the levosimendan group vs. 288 of 1054 [27.3%] in the dobutamine group, RR = 0.72, 95% CI 0.53–0.96, $p = 0.03$, $Q = 15.67$, p for heterogeneity = 0.15, $I^2 = 30\%$, NNT = 16 with 12 studies included), so was that in subgroup of patient's number greater than 100 and in multi-center subgroup. This also implies that more large sample and multi-center clinical studies are needed to evaluate the efficacy of the two drugs, especially in cardiology setting.

Concomitant use of β -blocker therapy has been encouraging, because a lot of patients with ischemic cardiomyopathy or chronic HF receive a β -blocker and β -blockers are recommended as first-line therapy by the guidelines.²³ Owing to adverse effects of β -blocker therapy on the hemodynamic response to dobutamine,²⁴ patients with HF receiving β -blocker therapy usually require higher doses of dobutamine to assure its efficacy.

In contrast, levosimendan still efficiently improves cardiac contractility during the concomitant use of

β -blocker therapy.²⁵ Moreover, a subanalysis in the LIDO study showed that the effect of dobutamine on cardiac output was attenuated for concomitant use of β -blockers, but the effect of levosimendan was not affected.²⁶ Our study firstly confirmed these results from the perspective of the prognosis, and this has not been found previously in other meta-analysis about levosimendan vs. dobutamine. Thus, levosimendan may be the better choice than dobutamine in the treatment of HF during long-term maintenance therapy with β -blockers. Although the dataset of subanalysis on sepsis is small (only including three studies), the outcome is noteworthy. As severe sepsis usually produces low systemic vascular resistance, the beneficial effect of levosimendan may be neutralized to some extent by its vasodilator effect on critically ill patients with severe sepsis or septic shock. Clinicians should assess the cause of shock more carefully. If low systemic vascular resistance accounts for much of effects in circulatory failure, levosimendan should not be selected in patients with severe sepsis or septic shock. The outcomes of subanalysis about different follow-up times should be paid close attention to. The survival benefit from levosimendan was only found in studies with short-term follow-up (≤ 30 d). The outcome in studies with the longest follow-up of at least 90 d or 180 d was still unsatisfactory.

The effect of levosimendan vs. dobutamine on long-term prognosis has yet to be studied further.

The result of subanalysis about infusion rate in study seems to be inconsistent with that in the study of Landoniet *al.*¹³ Although Landoniet *al.*¹³ reported positive results in both subgroups of patients receiving an infusion rate ≤ 0.1 and $> 0.1 \mu\text{g}/\text{kg}/\text{min}$, a trend towards an increased survival was also found in the subgroup of patients receiving an infusion rate $\leq 0.1 \mu\text{g}/\text{kg}/\text{min}$.²¹

CONCLUSION

This study shows that levosimendan is more effective in maintaining hemodynamic stability in critically ill patients and supports failing heart by increasing blood pressure, cardiac output, and keeps cardiac index within normal range. Yet further studies are required to compare the effects of these two drugs on long-term survival.

Conflict of interest: None

Authors' contribution:

DJ: Concept, conduction of study

SL: Conduction of study, manuscript editing

DC & MC: Conduction of study, collection of data

DKS: Concept, data analysis, reviewing

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