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Effect of Levosimendan Versus Dobutamine in Patients with Acute Decompensated Heart Failure

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Abstract: ***Introduction:****Acute decompensated heart failure is one of the major contributors of mortality in the world. The immediate measures include therpy with diuretics and inotropic support. Levosimendan is a recently introduced inotrope which acts as a calcium channel sensitizer. This study the effect of treatment with Levosimendan versus Dobutamine in hospitalized patients with acute decompensated heart failure (ADHF) based on echocardiographic parameters.* ***Methods:****Present study included a total of 126 ADHF patients. They received 24 hrs intravenous infusions of levosimendan (n=63) or dobutamine (n=63) therapy. Echocardiographic parameters like LAVI, LVEDD, LVEF and PCWP were studied in these patients. The results were compared in both the groups.* ***Results:****Compared with baseline level, left ventricular ejection fraction (LVEF) in both groups increased significantly on 4th day(Levosimnedan;25.7% versus 29.97%, P<0.01 and dobutamine;28.33% versus 30.87%, P<0.01). The PCWP also increased significantly in both groups on 4th day (Levosimnedan;44.03% versus 26.87%, P<0.01 and dobutamine;44.05% versus 26.13%, P<0.01). The LVIDP also decreased significanltly in both the groups with p value <0.01.The change rate of LaVI was insignificant in both the groups with p value >0.01. The incidences of adverse reactions and events were similar between two groups.* ***Conclusion:*** *In patients with ADHF, levosimendanimproved haemodynamic parametersas effectively as dobutamine. In our study LaVI did not decrease significantly with bothlevosimendan and dobutamine. Tolerability and safety were similar between domestic levosimendan and dobutamine.*

Keywords: *Levosimendan, Dobutamine; Acute decompensated heart failure; Haemodynamic effect*

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I. Introduction

Levosimendan is a new inotropic agent and calcium sensitizer which has been found to increase myocardial contractility via a sensitization of cardiac troponin C to calcium, to produce vasodilatation and cardioprotection by opening scarolemmal and mitochondrial ATP-sensitive potassium channels in vascular smooth muscle cells respectively and to inhibit phosphodiesterase type III[1]. Now, levosimendan has been approved to treat Acute Decompensated Heart Failure (ADHF) in guidelines and widely used in clinical practice for the treatment of heart failure in different settings since year 2000.

II. Material &Methods

Study population

126 patients between 18-75 years old with ADHF of ischemic or non ischemic origin, in New York Heart Association (NYHA) class III–IV, with left ventricular ejection fraction (LVEF) ≤ 40%, admitted in our hospital were enrolled. All patients were randomized into levosimendan group (63 patients) and dobutamine group (63 patients).

Inclusion criteria:

- Age >18 years
- Both males and females

ADHF of ischemic or non ischemic origin, in New York Heart Association (NYHA) class III–IV, with left ventricular ejection fraction (LVEF) ≤ 40%,

Exclusion Criteria:

- Systolic blood pressure (SBP) >180 mmHg or <90 mmHg,
- malignant arrhythmia,
- valvular heart disease,
- hypertrophic and restrictive cardiomyopathy,
- acute coronary syndrome during 1 week before baseline,
- severe liver or renal dysfunction,
- severe pulmonary disease.

Treatment Protocol:

All patients received optimized conventional treatment for HF. Levosimendan group: Levosimendan was firstly administered as an initial loading dose of 12 μg/kg delivered over 10 min and then followed by a continuous intravenous infusion of 0.1 μg/kg/min for 2 hours. The levosimendan infusion rate was increased to 0.2 μg/kg/ min for further 22 hours if no Dose-Limiting Events (DLEs) occurred. Dobutamine group: Dobutamine was administrated as a continuous infusion without a loading dose, beginning at a rate of 2 μg/kg/min for 2 hours, and then increased to 4 μg/kg/min for further 46hours. After the therapy, patients received observation for 5-7 days in hospital. During this period, echocardiographic parameters were evaluated.

Echocardiographic Evaluation

All patients were evaluated by using Philips HD15 with 2.5 MHz probe. Echocardiographic parameters such as LAVI, LVEDD, LVEF and Pulmonary Capillary Wedge Pressure (PCWP) was measured on the day of admission and on the 4^{th} day after admission. LVEF was measured using the Simpsoms method.PCWP was calculated using the Naguehformula.

Statistical methods

Quantative variables are expressed as mean value $\pm$ standard deviation for parametric variables and median and range for non-parametric variables. Comparisons of parametric values among the groups will be performed by one-way analysis of variance. Chi-square test will be used for analysing the association of different variables of the study and SxS. The t – test of difference will be used between the means of both the groups.

III. Results

In our study the male patients were 74% and female patients were 26%. In the 76 patients with hypertension significant improvement was found in PCWP, ejection fraction and Left Ventricular Internal Diameter during Diastole (LVIDP) ($p < 0.01$) where as LaVI reduction was insignificant in the non hypertensive group(50). In the 59 patients with Diabete mellitus significant improvement was found in PCWP, ejection fraction and LVIDP($p < 0.01$) where as LaVI reduction was insignificant in the non diabetic group(67). In the 22 patients with CAD significant improvement was found only in PCWP reduction ($p < 0.01$). In the 59 patients who were smokers significant improvement was found in PCWP reduction and ejection fraction ($p < 0.01$). In the 47 patients who were alcoholic significant improvement was found in PCWP reduction and ejection fraction ($p < 0.01$). Patients who were previously on beta blockers had better reductions in PCWP. Compared with baseline level, left ventricular ejection fraction (LVEF) in both groups increased significantly on 4th day(Levosimnedan;25.7% versus 29.97%, P<0.01 and dobutamine;28.33% versus 30.87%, P<0.01). The PCWP also increased significantly in both groups on 4^{th} day (Levosimnedan;44.03% versus 26.87%, P<0.01 and dobutamine;44.05% versus 26.13%, P<0.01). The LVIDP also decreased significanltly in both the groups with p value <0.01.The change rate of LaVI was insignificant in both the groups with p value >0.01. The incidences of adverse reactions and events were similar between two groups.

Table 1: Comparison of Echo Parameters in both the groups.

Echo parameters	Dobutamine(n=63)				P-Value
	Before		After		
	Mean	SD	Mean	SD	
LVIDd	5.98	0.53	5.58	0.80	0.0012
LaVI	139.60	18.45	137.30	18.61	0.48 NS
PCWP	44.05	6.21	26.13	8.84	0.0001
EF	28.33	4.16	30.87	4.85	0.002

Echo parameters	Levosimendan(n=63)				P-Value
	Before		After		
	Mean	SD	Mean	SD	
LVIDd	6.03	0.48	5.69	0.81	0.004

LaVI	147.44	44.02	139.51	34.15	0.26 NS
PCWP	44.03	7.69	26.87	10.52	0.0001
EF	25.71	5.24	29.97	4.90	0.00001

IV. Discussion

Levosimendan is a novel calcium sensitizer, which has inotropic effect by increasing sensitivity of Ca^{2+} in the contraction site. Levosimendan could improve myocardial contractility without increasing intracellular cyclic Adenosine Monophosphate (cAMP) or Ca^{2+} concentration[2].Butlevosimendan does not affect heart rate and increase myocardial oxygen consumption. In addition, the inotropic effect of levosimendan is not affected by β blockers, so that levosimendan could be used accompanied by β blockers[3].

Short-term use of levosimendan has been shown to cause rapid dose-dependent improvement in hemodynamics and symptoms in patients with decompensated heart failure [4,5].

The LIDO study showed that levosimendan may improve the hemodynamic of acute heart failure and 180-day survival rate more effectively[6].

González et al. found that levosimendan improvedhaemodynamic parameters in critically ill patients with reduced LVEF[7].

A hemodynamic improvement (increase in cardiac output and decrease in PCWP) was associated with a lower mortality at one- and six-months with levosimendan compared to dobutamine[8].

In our study compared with baseline level, left ventricular ejection fraction (LVEF) in both groups increased significantly on the 4th day of admission. The PCWP also increased significantly in both groups on 4th day of admission. The LVIDP also decreased significantly in both the groups with p value <0.01.The change rate of LaVI was insignifanct in both the groups with p value >0.01. The incidences of adverse reactions and events were similar between two groups. In the 22 patients with CAD significant improvement was found only in PCWP reduction (p <0.01).Similarly, in the Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct (RUSSLAN) trial, levosimendan did not cause hypotension or clinically significant ischemia. Levosimendan also reduced the risk of worsening heart failure and death[9].In general, levosimendan could do better in improving hemodynamics in ADHF patients, improving cardiac output while reducing pulmonary congestion, and reducing the circulation resistance.

Previous studies have shown that levosimendan also could improve hemodynamics in patients with chronic heart failure, increase cardiac contractility and dilate blood vessels[10]. The SURVIVE study[11]enrolled 1327 cases of acute heart failure patients, and the results showed that levosimendan had significantly greater decrease in BNP level after administration of 24 hours than dobutamine.The Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE-II) study showed that levosimendan was associated with more adverse effects like hypotension and cardiac arrhythmias while providing improvement in symptoms in acutely decompensated heart failure patients[12]. Research by Parissis[13] showed that levosimendan significantly reduced NT-proBNP level and tumor necrosis factor-α level, but no such changing in dobutamine group before and after treatment.

In our study patients who were on beta blocker therapy prior to admission had better improvement in hemodynamic parameters compared with those not on beta blocker therapy. Previous studies by Berg CH et al showed similar findings[14].Recent European Society of Cardiology (ESC) guidelines for the treatment of patients with acute heart failure recommend that intravenous levosimendan may be considered to reverse the state of hypoperfusion caused by β-blockers[15]. Although these trials are available, the safety and clinical efficacy of levosimendan has not been well established in these patients and hence further studies with larger coharts are needed.

V. Conlusion

In summary, the results of this study revealed that the domestic levosimendan had better effects on reducing PCWP, increasing cardiac output and reducing SVR than dobutamine.

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