International Journal of Cardiology 168 (2013) 237–242

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Facilitation of left ventricular function recovery post percutaneous coronary intervention by levosimendan

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ARTICLE INFO

Article history:
Received 28 January 2012
Received in revised form 25 May 2012
Accepted 15 September 2012
Available online 11 October 2012

Keywords:
Levosimendan
Hibernation
Heart failure
PCI

ABSTRACT

Background: Efficiency of percutaneous revascularization and the utility of levosimendan for advanced ischemic heart failure (HF) is unclear. We examined the efficacy of revascularization and levosimendan on left ventricular ejection fraction (LVEF) and mortality of patients admitted with acute decompensated HF and severe left ventricular dysfunction.

Methods: A prospective case control study that enrolled 84 patients with ischemic decompensated HF with LVEF <35% and preserved LV wall thickness. Group A: 42 patients whose LVEF improved post percutaneous coronary intervention (PCI). Group B1: 22 patients whose LVEF did not improve post-PCI alone but improved after levosimendan. Group B2: 20 patients whose LVEF did not improve neither post-PCI nor post levosimendan.

Results: LVEF increased in group A from 22±5 to 29±5% post PCI and continued to improve at the 6 month follow-up (36±4%). In group B1 LVEF did not improve after PCI, but increased after levosimendan from 23±4% to 32±4% and remained constant at 6 months. In group B2 LVEF 26±4% did not change following both interventions.

Reverse remodeling with a decrease in end-diastolic and end-systolic diameters was observed only in groups A and B1.

Group B2 had a dismal prognosis with 36% in-hospital and 43% six month mortality. Groups A and B1 had a lower in hospital (4.7%, 4.5%) and mid term (11%, 11%) mortality.

Conclusion: Improvement of LV size and function with better prognosis can be expected in the majority of patients undergoing PCI for decompensated ischemic HF. Levosimendan enhanced the recovery of LV function post PCI.

1. Introduction

Physicians usually encounter difficult decisions concerning coronary intervention in patients with reduced left ventricular systolic function and heart failure. The ability to counterbalance the promising, but not completely certain, benefits of revascularization with the greater than usual peri procedural risks in this population is confounded by the absence of completed randomized trials and the inadequacy of the existing scientific literature [1].

Contemporary operation decisions are based largely on surgical studies performed nearly two decades ago. In the two largest series, Coronary Artery Surgery Study registry (420 medical patients and 231 surgical patients) [2] and Duke University Cardiovascular Database (409 medical patients and 301 surgical patients) [3], CABG provided a significant long-term survival advantage over medical therapy. The recent published STICH trial did not support these findings [4].

More recently the mode of revascularization in the presence of reduced LV function was evaluated [5–8]. Apparently similar long term survival and improvement in LV function can be expected. Late outcome after PCI or CABG was influenced primarily by the completeness and not the mode of revascularization.

Diastolic dysfunction is typically present in patients with ischemic cardiomyopathy, and is associated with worse hemodynamics, clinical status, and prognosis. LV diastolic filling may largely improve after revascularization and effects of levosimendan on diastolic function have been observed [9–11].

It has long been recognized that the phenomena of myocardial stunning and hibernation may prevail post revascularization [12]. Assessment of LV function shortly after revascularization may underestimate the beneficial effect of the procedure and reduce its ability to predict future clinical events. Moreover the influence of stunning/hibernation on the prognosis of patients post myocardial revascularization has never been evaluated.

Levosimendan is a novel agent developed for the treatment of acute and decompensated heart failure. Levosimendan has demonstrated the ability to sensitize myofibrils to calcium ions, open KATP channels and

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http://dx.doi.org/10.1016/j.ijcard.2012.09.088

inhibit the PDE III enzyme. All of these effects finally conduct to positive inotropy, lusitropy and vasodilation [13]. In an experimental study in dogs, levosimendan improved regional contractile function of stunned myocardium following reperfusion [14].

The aim of the present study was to examine the efficiency of revascularization by PCI for patients with decompensated heart failure to improve left ventricular function and the additive value of levosimendan on improvement of the stunned/hibernated myocardium. The primary endpoint was 6 months mortality and the secondary endpoint was the change in left ventricular function.

2. Methods

2.1. Study design and patient selection

This was a prospective case control descriptive study that enrolled consecutive patients between January 2007 and April 2011. The patients presented acutely to our department with decompensated heart failure and with severely reduced left ventricular function due to ischemic heart disease. To be eligible for this study, patients must suffer from severe systolic heart failure [New York Heart Association (NYHA) Classes III and IV] with a left ventricular ejection fraction (LVEF) ≤35% and be on individually optimized neurohormonal background therapy according to the guidelines for the treatment of chronic heart failure.

The patients must have at least one of these inclusion criteria: presented to hospital with acute coronary syndrome, proof of ischemia by dobutamine stress echocardiography or wall thickness of ≥7 mm in the territory supplied by the treated artery.

All patients underwent coronary catheterization and a percutaneous coronary intervention was performed. Echocardiography studies were performed before PCI, the day after PCI, repeated evaluation as required including following 6 months at follow-up.

Patients were divided into two groups. Group A included patients whose left ventricular ejection fraction (LVEF) improved in the day post PCI. Group B included patients whose LVEF did not improve the day post PCI. Thereafter group B patients were treated by infusion of levosimendan for 24 h and a repeat echocardiography was performed 24 to 48 h post levosimendan infusion.

We analyzed the change in global and regional wall motion abnormalities, using 16 segments for the evaluation of regional wall motion abnormality. This model consists of 6 segments at both basal and midventricular levels and 4 segments at the apex. Diastolic function examined by Doppler echocardiography of the mitral valve inflow was classified on two groups. Mild diastolic dysfunction included impaired relaxation pattern which was diagnosed when deceleration time of the E wave was >240 ms and E/A<1 and pseudonormal pattern which was diagnosed when deceleration time of E between 160 and 240 ms and E/A ratio 1–1.5. Severe diastolic dysfunction included restrictive pattern of mitral valve inflow which was documented when deceleration time of the E wave was less than 150 ms and E/A>1.5.

Levosimendan infusion was given by continuous infusion according to the recommended protocol but avoiding loading dose. We started with a rate of 0.05 μg/kg/min with gradual up-titration of the infusion according to blood pressure and heart rate to the middle dosage of 0.1 μg/kg/min and followed to the highest dosage of 0.2 μg/kg/min until completion of the target total dose of 12.5 mg. In all patients the infusion of levosimendan was completed within 24 h. All the patients were monitored for blood pressure and ECG changes in the intensive cardiac care unit during the levosimendan infusion and for 24 h after the completion of the dose. Nitroglycerin infusion and inotropic agents were not given during the administration of levosimendan.

The echocardiography was performed using Vivid 3,5,9 (General Electric) as available. End diastolic diameter (EDD) and end systolic diameter (ESD) were measured in long axis parasternal view using M mode at the level of the tip of papillary muscles. For analysis of global LV function we used Simpson's rule.

Regional contractile function was evaluated by visual assessment. Five standard views of the left ventricle were recorded: parasternal long, short-axis views, apical two, apical three and four-chamber views. The left ventricle was divided into 16 segments according to the ASE guidelines (2005) recommended model for LV segmentation. This model consists of 6 segments at both basal and midventricular levels and 4 segments at the apex. Each segment was evaluated as Hyperkinetic, Normal, Hypokinesis (decreased endocardial excursion and systolic wall thickening), Akinesis (absence of endocardial excursion and systolic wall thickening) and Dyskinesis (paradoxic outward movement in systole). The number of segments with impaired function was recorded as regional wall motion abnormality score.

Pulmonary artery pressure was evaluated using the continuous wave Doppler echocardiography, calculation of a trans tricuspid gradient from the maximal velocity of tricuspid regurgitation jet using the simplified form of the Bernoulli equation: DP (mm Hg) = 4 V^2 ($m \cdot s^{-1}$), right atrial pressure was estimated in two modes, first mode performed in all the patients by the severity of TR (add for Mild TR = 5 mm Hg, Mod TR = 10 mm Hg, Severe TR = 15 mm Hg), in the second mode for right atrial pressure estimation in 73% of patients we used IVC size and collapsibility (IVC was not visualized in all patients due to technical difficulties and patient's condition).

The severity of mitral valve incompetence was evaluated by echo Doppler and was graded as mild, moderate and severe. We used two methods for the grading of mitral regurgitation (MR) severity, the first method was calculation of the regurgitant jet area (RJA) expressed as a percentage of the left atrial area (LAA). RJA/LAA under 20% was defined as grade I mild mitral regurgitation, between 20% and 40% grade II moderate mitral regurgitation, and over 40% grade III severe mitral regurgitation. The second method was measuring the width of the vena contracta at the long axis parasternal view. A vena contracta width (VCW) of <0.3 cm denotes mild MR, whereas 0.3 cm>VCW<0.8 cm defines moderate MR and a cut-off above 0.8 cm classifies severe MR.

The primary end point of the study was all-cause mortality in hospital and during the 180 days following the index hospitalization. Secondary end points included changes in LV function from baseline to 24 h after revascularization or after infusion of levosimendan, and LV function six months post-index hospitalization.

2.2. Statistics

Chi-square tests for categorical data were applied for the comparison between groups, and the Fisher exact test when cell expected frequencies were low. Before vs after continuous data were compared by the paired t-test and ANOVA was used for the comparison between groups. P-values were adjusted for multiple comparisons. Kaplan–Meier curves were constructed for survival data and compared by the log rank tests. All P values were 2 sided. Statistical analysis was performed with the software SAS (version 9.2).

3. Results

Eighty-four patients with severely reduced left ventricular function, and decompensated heart failure who were admitted acutely to our cardiovascular department were recruited. The mean age of the patients was 73 years (range 52 to 89); their mean body weight was 76 kg (range 59 to 105); fifty three male patients and thirty one female patients were included.

All the patients received clopidogrel, a beta-blocker, diuretics and heparin, eighty three patients received aspirin, eighty patients received angiotensin converting enzyme inhibitors or angiotensin receptor blockers, forty three patients received calcium antagonists from the dihydropyridine group. Forty two patients had hypertension, and 39 patients were current smokers. Twenty three patients had diabetes, seventeen patients were taking oral hypoglycemic and fourteen patients received insulin routinely.

In addition to acute decompensation of chronic heart failure twenty-two patients had NSTEMI and ten patients had unstable angina.

All the patients underwent percutaneous coronary intervention. Left main stenosis was treated in ten patients, LAD was treated in fifty one patients, treatment of RCA was achieved in fifty four patients and CX was opened in forty three patients. The median of the treated lesions was 1.8 lesions per patient. Treatment of lesions with stenoses of more than 95% by visual assessment was performed in 94 lesions and in the rest 54 lesions 70–95% stenoses were treated.

Forty two patients showed improvement of LV systolic function the day after PCI and are included in group A. The other 42 patients did not improve their LV function 24 h post PCI and were given levosimendan (group B). Of them twenty two patients showed improved LV function 24 h post levosimendan infusion (group B1) while group B2 includes 20 patients whose LV function did not improve. There were no differences between the three groups in any of the patient clinical characteristics (Table 1).

3.1. Influence on systolic function

The quantitative assessment of regional left ventricular motion was done by counting the number of hypokinetic/akinetic/dyskinetic segments as the score.

The total number of hypokinetic or akinetic segments in group A decreased significantly after PCI, from 8.1 ± 0.8 to 4.9 ± 0.7 (P<0.001). In group B1 it decreased after levosimendan from 9.1 ± 0.9 to 6.3 ± 0.7 (P<0.001). In group B2 it did not change significantly from the baseline value of 8.3 ± 0.7 to 8.2 ± 0.8 (P = 0.79) after levosimendan (Fig. 1).

The left ventricular ejection fraction (LVEF) increased in group A from 22 ± 4% at baseline to 29 ± 4% one day after PCI (P = 0.01) and continued to improve at the six month follow-up to 36 ± 4% (P = 0.01). In group B1 LVEF was not improved the day after the PCI, but it increased significantly the day after levosimendan infusion from 23 ± 4% to 32 ±