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Original article

Utility of the neutrophil to lymphocyte ratio for predicting in-hospital mortality after levosimendan infusion in patients with acute decompensated heart failure

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ABSTRACT

Background: The aim of this study was to investigate the effect of a levosimendan infusion on hematological variables in patients with acute decompensated heart failure (ADHF). The predictive value of these variables for in-hospital mortality was also evaluated.
Methods: A total of 553 patients (368 males; mean age, 63.4 ± 14.9 years) with acute exacerbations of advanced heart failure (ejection fraction ≤35%) and treated with either dobutamine or levosimendan were included in this retrospective analysis. The patients that received levosimendan therapy were divided into two groups according to in-hospital mortality: group 1 (21%) included patients who died during hospitalization ($n = 45$), while group 2 (79%) included patients with a favorable outcome ($n = 174$) after levosimendan infusion. Changes in several hematological variables between admission and the third day after levosimendan infusion were evaluated.
Results: The demographic characteristics and risk factors of the two groups were similar. A comparison of changes in laboratory variables after the infusion of levosimendan revealed significant improvement only in those patients who had not died (group 2) during hospitalization. The neutrophil to lymphocyte (N/L) ratio after levosimendan infusion was an independent predictor of in-hospital mortality (odds ratio: 1.310, 95% CI: 1.158–1.483, $p < 0.001$). In a receiver-operating characteristic curve analysis, a value of 5.542 for the N/L ratio after levosimendan administration was identified as an effective cut-off point for predicting in-hospital mortality (area under the curve = 0.737; 95% confidence interval = 1100–1301; $p < 0.001$).
Conclusions: Levosimendan treatment was associated with significant changes in hematological variables in patients with ADHF. A sustained higher N/L ratio after levosimendan infusion is associated with an increased risk of in-hospital mortality in patients with ADHF.

Introduction

Heart failure (HF) is a complex syndrome rather than an exclusive problem of low cardiac output. Neurohormonal and inflammatory activation, particularly involving polymorphonuclear leukocytes, is thought to play a key role in the pathophysiology of HF [1]. An association between increased white blood cell (WBC) counts and a high incidence of HF-related hospitalization and mortality has been reported [2,3]. Additionally, the neutrophil-to-lymphocyte (N/L) ratio is a well-known prognostic marker in patients with coronary artery disease or in those undergoing coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting [4,5]. In parallel, neutrophilia has been found to be associated with an increased incidence of acute decompensated HF (ADHF) in patients with acute myocardial infarction [6], while relative lymphocytopenia has been shown to be an independent predictor of mortality in HF patients [7–10]. Recently, a higher N/L ratio on hospital admission was shown to be associated with an increased risk of short- and long-term morbidity and mortality in patients with ADHF [11].

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Levosimendan, a Ca^{2+} sensitizer that increases troponin-C sensitivity to cytoplasmic Ca^{2+} without modifying the intracellular Ca^{2+} density, improves cardiac performance and decreases systemic and vascular resistance and proinflammatory marker levels [12–16]. However, no data exist regarding the effect of a levosimendan infusion on the N/L ratio and its utility in predicting in-hospital mortality for patients with ADHF. The aims of this study were to evaluate the effects of levosimendan infusion on hematological variables and the association between the N/L ratio after levosimendan infusion and in-hospital mortality in patients with ADHF. We also compared the discriminative prognostic efficacy of these hematological variables with that of other variables at baseline and after the infusion of levosimendan. To our knowledge, our study is the first to investigate the effects of levosimendan on the WBC count and the prognostic value of the N/L ratio after levosimendan infusion in ADHF patients.

Materials and methods

Patient population

We retrospectively evaluated a total of 1061 consecutive patients who were admitted (from January 2011 to April 2013) to Bezmialem Foundation University Hospital (Istanbul) and Mehmet Akif Ersoy Thoracic-Cardiovascular Surgery Training and Research Hospital (Istanbul) with ADHF [ejection fraction $\leq$ 35% and New York heart Association (NYHA) Class IV]. Patients were analyzed in two groups according to positive inotropic treatment that they had received such as, levosimendan or dobutamine. Patients with medical conditions known to affect the total and differential WBC counts, such as: disorders of the hematopoietic system, history of cancer and/or previous treatment with chemotherapy, infection, and chronic inflammatory conditions; glucocorticoid therapy and/or histories of glucocorticoid use 3 months before the admission; and acute myocardial infarction or coronary revascularization within the past 6 months; and patients with incomplete data were excluded from the study. Also, patients who did not have both WBC counts before and after levosimendan infusion were excluded (Fig. 1). The study protocol was approved by the hospitals' ethics committees.

Analysis of patient data

Data included demographic characteristics, laboratory data, medications, and echocardiographic parameters collected by the study personnel from the hospitals' medical records. Clinical risk factors such as age, sex, diabetes mellitus (DM), hypertension (HT), hypercholesterolemia, smoking, and history of cardiovascular disease were determined. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. The left ventricular end systolic and diastolic diameters (LVESD, LVEDD), and ejection fraction (LVEF) measured before and after levosimendan therapy with transthoracic echocardiography were recorded. Complete blood counts which included total WBCs, neutrophils, and lymphocytes, and routine biochemical tests results were obtained and N/L ratio was calculated as the ratio of the neutrophil to lymphocytes, from the same automated blood sample before and after levosimendan infusion on the third day. Also, the serum high sensitivity C-reactive protein (hsCRP) levels, which were obtained with the nephelometric method, using a Dade Behring Cardio Phase kit (Dade Behring Inc., Newark, DE, USA) were recorded on admission and after levosimendan infusion. Death from any cause during hospitalization was the primary end point. Association between proportion of changes in hematological variables after levosimendan infusion were evaluated. Additionally, the independent association of different hematological variables with in-hospital mortality was analyzed.

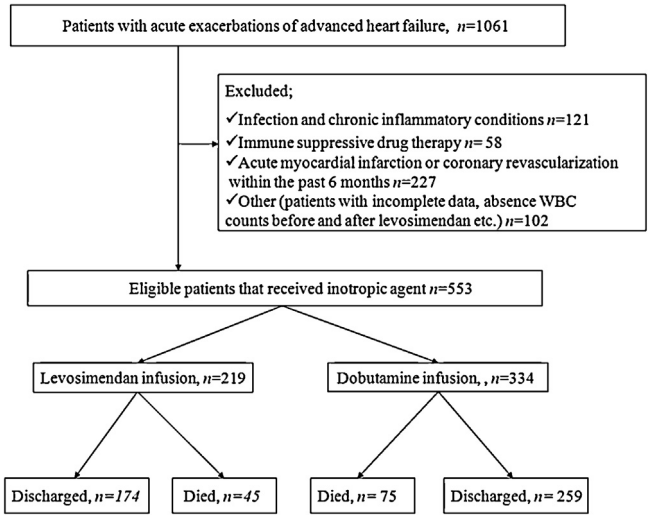

Fig. 1. Flow chart of the patients enrolled in the study. WBC, white blood cell.

Statistical analyses

Categorical variables were expressed as frequencies and percentages. Chi-square tests were used to compare categorical variables. Univariate and a backward stepwise multivariate logistic regression analysis, was performed to evaluate the independent predictors of in-hospital cardiovascular mortality. To analyze the association of ΔN/L ratio with in-hospital mortality, continuous variables were compared using analysis of covariance when baseline variables were presumed as a covariate for those with skewed distributions. A logistic regression model was used to analyze the independent association of ΔN/L ratio. The Kaplan–Meier curve and log-rank test were used to compare time to event distributions. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

A total of 219 consecutive eligible patients (mean age, 63.2 ± 12.7 years; 168 males, 51 females) that received levosimendan were included in this retrospective study. Also, 334 patients that underwent dobutamine therapy were analyzed as a control group. After the levosimendan infusion, a significant increase in the LVEF (26.7 ± 5.8% *vs.* 29.2 ± 5.4%, $p < 0.001$) and lymphocyte count (1.3 ± 0.7 × 1000/μl *vs.* 1.5 ± 0.7 × 1000/μl, $p = 0.03$) and significant decreases in the LVESD (49.1 ± 4.9 cm *vs.* 47.1 ± 4.5 cm, $p = 0.02$), WBC count (9.6 ± 3.7 × 1000/μl *vs.* 9.2 ± 3.8 × 1000/μl, $p = 0.02$), neutrophil count (7.2 ± 3.6 × 1000/μl *vs.* 6.8 ± 3.7 × 1000/μl, $p = 0.004$), hsCRP (7.6 ± 4.8 ng/ml *vs.* 5.9 ± 3.1 ng/ml, $p < 0.001$), and creatinine level (1.3 ± 0.5 mg/dl *vs.* 1.2 ± 0.5 mg/dl, $p = 0.005$) were observed (Table 1). However, favorable changes in hematological variables were not seen in patients that received dobutamine therapy (Table 1). The patients that received levosimendan infusion were divided into two groups according to in-hospital mortality: group 1 (21%) included patients who died during hospitalization ($n = 45$), while group 2 (79%) included patients with a favorable outcome ($n = 174$) after levosimendan infusion. The demographic characteristics and risk factors of the two groups were similar (Table 2). There was no significant difference in the medications that the patients received during hospitalization. An analysis of laboratory