Levosimendan and Nesiritide as a Combination Therapy in Patients With Acute Heart Failure

Zhi Jia, MS, Mu Guo, MS, Li-Yuan Zhang, MS, Yun-Qiang Zhang, PhD, Hai-Qing Liang, MS and Yu Song, MS

Abstract: *Background:* Individually, levosimendan and nesiritide have been associated with substantial clinical benefits for the treatment of acute decompensated heart failure (ADHF). The aim of this study was to evaluate the efficacy of the combination of levosimendan and nesiritide for the treatment of ADHF. *Methods:* One hundred and twenty patients were randomly assigned to control, levosimendan, nesiritide or combination groups. The patients received 2 drugs: 1 was levosimendan or placebo A and the other was nesiritide or placebo B. The primary end points were rates of clinical effectiveness at 1, 3, 5 and 9 days after the start of therapy. *Results:* Nine days after the initiation of drug infusion, the clinical effectiveness rate in the combination group was better than that in the control group (odds ratio: 1.43, 95% confidence interval: 0.46–2.41, $P = 0.004$). The combination treatment also resulted in higher rates of clinical effectiveness than individually provided levosimendan or nesiritide at 1 day (both $P = 0.04$) or placebo at 1, 3 or 5 days ($P = 0.002$, 0.006 and 0.009, respectively). The combination method was associated with fewer deaths and readmissions, as compared with the rate observed in the placebo group during the 3-month follow-up (hazard ratio: 0.43, 95% confidence interval: 0.19–0.96, $P = 0.038$). *Conclusions:* Among patients with ADHF, intravenous infusion of levosimendan and nesiritide was superior to placebo and single-drug therapies in terms of improvements in clinical conditions during the early stages of therapy.

Key Indexing Terms: Heart failure; Nesiritide; Levosimendan; Ventricular function. **[Am J Med Sci 2015;349(5):398–405.]**

It has previously been demonstrated that nesiritide may protect the heart from injury and inhibit unfavorable remodeling after injury.[1] Nesiritide (B-type natriuretic peptide, BNP) is a small endogenous cardiac peptide that is used to confirm diagnosis and aid in assessments of prognosis in cases of heart failure. Nesiritide results in coronary vasodilatation with a reduction in myocardial oxygen consumption,[2] enhancement of myocardial relaxation[3] and inhibition of renin-angiotensin-aldosterone system activation.[4] Importantly, nesiritide (human recombinant BNP) is safe and effective for the treatment of acute decompensated heart failure (ADHF)[5,6] and has been included in the 2013 ACCF/AHA Guideline for the Management of Heart Failure and the HFSA 2010 Comprehensive Heart Failure Practice Guideline.[7,8] Moreover, levosimendan is a calcium sensitizer and a positive inotropic agent that increases the contractile force of the myocardium by enhancing the sensitivity of myofilaments to calcium without increasing the intracellular calcium concentration.[9] Therefore, it has been recommended by the European Society of Cardiology for the use in normotensive patients with acute systolic dysfunction in low-output heart failure.[10]

Recently, concerns have been raised about the effects of nesiritide and levosimendan on mortality. The ASCEND-HF trial has shown that nesiritide has minimal effects on survival.[11] However, levosimendan has been demonstrated to confer greater survival benefit than dobutamine or placebo.[12,13] Individually, however, nesiritide and levosimendan each have positive effects in terms of relieving patients' symptoms and improving heart function with decreasing BNP plasma levels.[14–19] For example, it has been reported that BNP levels decreased in patients with acute heart failure after therapy with nesiritide.[18,19] Similarly, levosimendan treatment leads to an initial increase in left ventricular ejection fraction (LVEF) and short-term reductions in BNP levels.[15–17,20] To date, however, studies have not examined whether the combination of nesiritide and levosimendan could produce a synergistic effect, resulting in a superior total efficacy and safety. In this study, a comprehensive evaluation of the effectiveness and safety of the combination of nesiritide with levosimendan to treat ADHF. Analysis is based on a clinical trial with a factorial experimental design.

METHODS

Patients

This randomized single-blind study enrolled a total of 120 patients with ADHF from the Heart Failure Program of TEDA International Cardiovascular Hospital, which is certified by the Certification for Clinical Care Programs. Additional blinding methods were designed for the examiners during hospitalization, as well as for investigators and interviewers at the end of the last follow-up. Patients were randomly assigned to the control, levosimendan, nesiritide or combination group (30 cases per group). Patients were included if they met both of the following clinical criteria. First, included patients had to have level III or IV cardiac function, as assessed using the New York Heart Association (NYHA) cardiac functional grading system. Second, included patients had to show 1 or both of the following symptoms, despite at least 24 hours of conventional therapies: (1) dyspnea at rest and/or the need for mechanical ventilation to treat ADHF or (2) oliguria that was not the result of hypovolemia. In addition, selected patients had to have an LVEF that was no more than 0.35, as shown by 2-dimensional echocardiography, and a BNP level higher than 400 pg/mL. The exclusion criteria were as follows: patients younger than 18 years, patients with childbearing potential, patients with heart failure because of restrictive or hypertrophic cardiomyopathy or uncorrected stenotic valvular disease, patients who suffered an acute myocardial infarction during the previous 14 days or a refractory angina at the time of randomization, patients with sustained ventricular

From the Coronary Care Unit, TEDA International Cardiovascular Hospital, Cardiovascular Clinical College of Tianjin Medical University, Tianjin, China.

Submitted November 18, 2014; accepted in revised form February 23, 2015.

M.G. has received a grant from the Tianjin Public Health Bureau (2011KZ18) and Y.S. is currently receiving a grant from the same organization (2013KZ006).

The remaining authors have no conflicts of interest to disclose.

Correspondence: Yu Song, MS, TEDA International Cardiovascular Hospital, 61 the Third Street, TEDA, Tianjin 300457, China (E-mail: johnbikzly@163.com).

tachycardia (SVT) or ventricular fibrillation (VF) or 2nd- or 3rd-degree atrioventricular block, patients with a resting heart rate of more than 120 beats per minute or a systolic blood pressure (SBP) below 85 mm Hg and patients with severe renal failure (serum creatinine >450 μmol/L), hepatic failure, cardiac tamponade, adult respiratory distress syndrome or septic shock.

Study Protocol

Patients were randomized into the 4 groups according to a computer-generated randomization schedule and were permitted to receive all appropriate therapy for the management of decompensated heart failure.[10] All groups received anticoagulants, aldosterone receptor antagonists, angiotensin-converting enzyme inhibitors, diuretics and other standard antiheart failure therapies under the same conditions. Additionally, patients received 2 drugs: 1 was levosimendan or placebo A and the other was nesiritide or placebo B (Figure 1). For the groups receiving nesiritide, an intravenous injection of 2 μg/kg was provided to start (a bolus injection was not provided if SBP was below 100 mm Hg), followed by a continuously injected intravenous dose of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the next 72 hours. However, a continuous infusion of levosimendan (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 24 hours) was administered to patients in the appointed group. All infusions were maintained at a constant rate for 24 or 72 hours, unless dose-limiting events occurred or the patient suffered a major cardiovascular event, suffered a serious adverse reaction or needed rescue therapy with intravenous inotropic or vasodilator agents. Vital signs, including electrocardiogram, blood pressure, heart rate, respiration rate, water intake and urine output, were monitored during drug infusions in the coronary care unit. Patients who developed persistent hypotension or refractory heart failure during the infusion were given intravenous dopamine, dobutamine and cedilanid or were treated with an intra-aortic balloon pump.

This study was conducted in accordance with the Declaration of Helsinki (World Medical Assembly) and its amendments and was approved by the Institutional Review Board of TEDA International Cardiovascular Hospital. Written informed consent was obtained from all participants before their enrollment in the study.

Assessments

Patient evaluations were performed at baseline (before treatment) and included a medical history, a physical examination, an echocardiogram and blood sampling to provide an assessment of standard laboratory variables, as detailed elsewhere. Dyspnea, pulmonary congestion, edema and NYHA functional class were assessed at baseline and at 1, 3, 5 and 9 days after the initiation of infusions of the investigated drugs. Plasma BNP levels and LVEF were measured again on the 5th day after the start of the infusion. Adverse events were assessed and calculated by the clinicians during the first 5 days of the study period. Additional inotropic support (including dopamine, norepinephrine or intra-aortic balloon pump) was also administered within 5 days. Survival was evaluated at the end of the 3rd month after the start of the infusions. The evaluations were reported and evaluated by the investigators who were unaware of patient treatment allocation at the time of assessment.

End Points

The primary end point was the proportion of patients in whom the treatment was clinically effective at 1, 3, 5 and 9 days after the start of the infusion. Clinical effectiveness was assessed based on 4 clinical parameters related to the patients' conditions: dyspnea, pulmonary congestion, edema and NYHA functional class. For each parameter, improvement was defined as a decrease of 1 or more classes from the baseline values. The

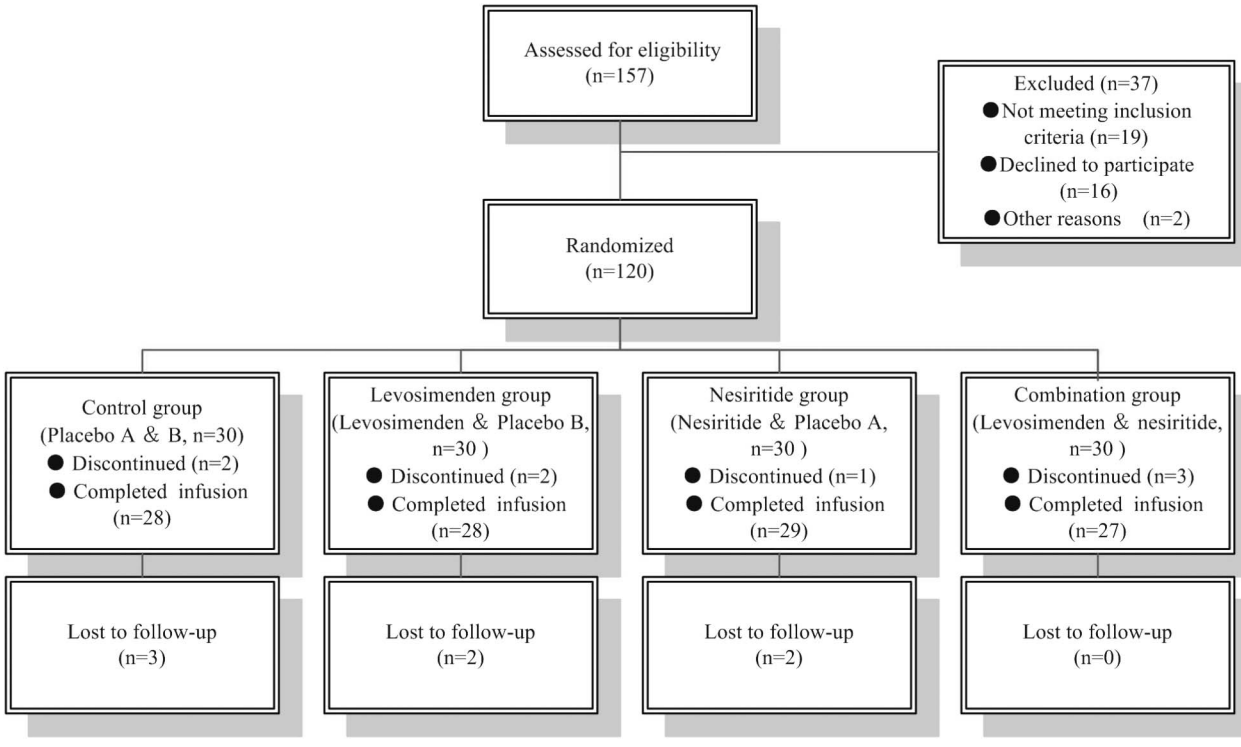

FIGURE 1. Participant flow through the study.