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CLINICAL RESEARCH

Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure

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Background This study evaluated the efficacy and safety of levosimendan, a positive inotropic drug with vasodilator effects, given intravenously to patients with acutely decompensated heart failure (ADHF).

Methods We performed 2 sequential trials, the first to develop a new measure of efficacy in 100 patients, and the second to use this measure to evaluate levosimendan in an additional 600 patients. Patients admitted with ADHF received placebo or intravenous levosimendan for 24 h in addition to standard treatment. The primary endpoint was a composite that evaluated changes in clinical status during the first 5 days after randomization.

Results In the 600-patient trial, more levosimendan than placebo patients (58 vs. 44) were improved at all 3 pre-specified time points (6 h, 24 h, and 5 days), whereas fewer levosimendan patients (58 vs. 82) experienced clinical worsening ($p = 0.015$ for the difference between the groups). These differences were apparent, despite more frequent intensification of adjunctive therapy in the placebo group (79 vs. 45 patients). Improvements in patient self-assessment and declines in B-type natriuretic peptide levels with levosimendan persisted for 5 days and were associated with reduced length of stay ($p = 0.009$). Similar findings were present in the 100-patient pilot trial. Levosimendan was associated with more frequent hypotension and cardiac arrhythmias during the infusion period and a numerically higher risk of death across the 2 trials (49 of 350 on a regimen of levosimendan vs. 40 of 350 on a regimen of placebo at 90 days, $p = 0.29$).

Conclusions In patients with ADHF, intravenous levosimendan provided rapid and durable symptomatic relief. As dosed in this trial, levosimendan was associated with an increased risk of adverse cardiovascular events. (Evaluation of Intravenous Levosimendan Efficacy in the Short Term Treatment of Decompensated Chronic Heart Failure; NCT00048425) (J Am Coll Cardiol HF 2013;1:103–11) © 2013 by the American College of Cardiology Foundation

More than 1 million people are hospitalized in the United States for the treatment of acutely decompensated heart failure (ADHF) each year (1), but the optimal management of these patients has not been defined. Patients generally receive immediate intravenous treatment with 1 or more drugs, including diuretics, peripheral vasodilators, and/or positive inotropes, which can produce rapid improvement in hemodynamic variables (2,3). However, it is not clear that these hemodynamic effects translate into clinical benefits (3,4). Many drugs that increase cardiac output and decrease cardiac filling pressures have not been shown to produce symptomatic benefits or improved outcomes (4–6).

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This apparent dissociation between the hemodynamic and symptomatic effects of intravenous drugs might partly reflect the difficulties inherent in designing, performing, and analyzing clinical trials in these acutely ill patients (7,8). Symptoms in ADHF are difficult to quantify and cannot be

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Abbreviations and Acronyms

ADHF = acutely decompensated heart failure

BNP = B-type natriuretic peptide

NYHA = New York Heart Association

readily assessed in a standardized fashion. Clinical trials have used a variety of instruments to assess dyspnea, with disappointing or conflicting results (4,6,9). To complicate matters further, nearly 80% of patients with ADHF improve after intensified standard treatment (6–8). Such intensification of background therapy (especially if applied differently across treatment groups) can make it difficult to discern the benefits of any new treatment. Finally, any acute improvement might not be sustained, and the clinical status of many patients might destabilize in the days and weeks after initial symptom relief (3,9,10). However, most trials have focused primarily on the response to drug interventions at a fixed point in time and have not determined the influence of the drug on the clinical course of patients (5,6,11).

To address these deficiencies, we carried out 2 sequential trials (REVIVE [Randomized EValuation of Intravenous LeVosimendan Efficacy] I and II), which first sought to develop a new measure of efficacy in patients with ADHF and then used this measure to evaluate the efficacy and safety of intravenous levosimendan. Levosimendan possesses positive inotropic and vasodilator properties (12), and in controlled trials in patients with ADHF, it has been reported to produce favorable effects on cardiac performance, symptoms, hospital stays, and survival (13–16). The hemodynamic effects of levosimendan persist for many days after a 24-h infusion, due to a long-lived active metabolite (17).

Methods

The REVIVE I and II trials were carried out in 103 centers in the United States, Australia, and Israel between December 2001 and December 2004 under the direction of an independent Steering Committee, which was responsible for the scientific aspects of the studies. An independent Data Monitoring Committee, comprising 4 cardiologists and a statistician, periodically reviewed (in an unblinded manner) the interim results and was empowered to recommend early termination of the program if a safety concern emerged during the studies. The studies were approved by the local ethics committees of each institution and were conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before participation in the studies.

Study patients. The REVIVE I and II trials enrolled patients who were hospitalized for the treatment of ADHF and remained dyspneic at rest despite treatment with intravenous diuretics. At randomization, patients might have also received intravenous vasodilators and/or positive inotropic drugs (except amrinone and milrinone), but the infusion rates of these drugs must have remained constant for at least 2 h before entry into the study. All patients had left ventricular dysfunction, evidenced by a left ventricular ejection fraction $\leq$35% within the prior 12 months.

Patients were excluded if intubated or otherwise unable to communicate; had a systolic blood pressure $\leq$90 mm Hg or a heart rate $\geq$120 beats/min; had experienced angina within 6 h or cardioversion within 4 h (or were expected to undergo cardioversion within 5 days); had significant uncorrected valvular obstruction, undergone a cardiac resynchronization procedure within 30 days, or had a stroke or transient ischemic attack or were expected to undergo cardiac revascularization or surgical procedures within 3 months; or had severe hepatic impairment (liver enzymes $>5\times$ the upper limit of normal), severe renal insufficiency (serum creatinine $>$5 mg/dl), severe obstructive pulmonary disease (carbon dioxide retention or ongoing use of steroids), acute bleeding or severe anemia (hemoglobin $<$10 g/l), active infection, serum potassium concentration $<$3.5 or $>$5.4 mmol/l, or a history of torsade de pointes.

Study plan. After initial evaluation, patients were randomly assigned (double-blind) to treatment with placebo or levosimendan, which was added to their existing management for ADHF. Randomization was stratified by the baseline use of positive inotropic and/or vasodilator agents. Treatment with the study medication (levosimendan or placebo) was initiated with an intravenous bolus of 12 μg/kg over 10 min (6 μg/kg if the patient was receiving concurrent intravenous vasodilator or positive inotropic agent) followed by a continuous intravenous infusion of 0.1 μg/kg/min. If tolerated, the infusion was increased after 50 min to 0.2 μg/kg/min and was maintained for 23 additional hours. If not tolerated, the infusion rate could be reduced to 0.05 to 0.1 μg/kg/min or treatment with the study drug could be discontinued. Patients were not aware of changes in hemodynamic variables (including blood pressure or heart rate), on the basis of concerns that knowledge of these might influence the assessment of their symptoms or clinical status.

After randomization, physicians could use any clinically indicated interventions, including initiation of new treatments or adjustment of concomitant medications. However, physicians carefully recorded the reasons for any use of medications or interventions and documented whether such use represented: 1) continuation of an existing strategy to maintain clinical improvement (referred to as "maintenance therapy"); or 2) intensification of treatment in a patient who was deteriorating clinically or failing to improve by 24 h on a regimen of conventional therapy (referred to as "rescue therapy"). Milrinone or amrinone were not permitted within 24 h of randomization.

At 6 and 24 h and after 2, 3, and 5 days after randomization, patients were asked to evaluate changes in overall clinical status (the patient global assessment) and in dyspnea. These changes were characterized as markedly, moderately, or mildly improved; unchanged; or mildly, moderately, or markedly worse. To do so, patients made a self-directed mark on the case report form, without assistance or prompting from study staff. In parallel, physicians independently rated the changes in the overall clinical status of patients. In addition, circulating levels of B-type natriuretic peptide (BNP) were