Clinical Trials

Intravenous Salt Supplementation With Low-Dose Furosemide for Treatment of Acute Decompensated Heart Failure

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ABSTRACT

Background: Theoretically, salt supplementation should promote diuresis through increasing the glomerular filtration rate (GFR) during treatment of acute decompensated heart failure (ADHF) even with low-dose furosemide; however, there is little evidence to support this idea.

Methods and Results: This was a prospective, randomized, open-label, controlled trial that compared the diuretic effectiveness of salt infusion with that of glucose infusion supplemented with low-dose furosemide in 44 consecutive patients with ADHF. Patients were randomly administered 1.7% hypertonic saline solution supplemented with 40 mg furosemide (salt infusion group) or glucose supplemented with 40 mg furosemide (glucose infusion group). Our major end points were 24-hour urinary volume and GFR. Urinary volume was greater in the salt infusion group than in the glucose infusion group ($2,701 \pm 920$ vs $1,777 \pm 797$ mL; $P < .001$). There was no significant difference in the estimated GFR at baseline. Creatinine clearance for 24 h was greater in the salt infusion group than in the glucose infusion group (63.5 ± 52.6 vs 39.0 ± 26.3 mL min^{-1} 1.73 m^{-2}; $P = .048$).

Conclusions: Salt supplementation rather than salt restriction evoked favorable diuresis through increasing GFR. The findings support an efficacious novel approach of the treatment of ADHF. (*J Cardiac Fail 2014;20:295−301*)

Key Words: Salt restriction, heart failure, glomerular filtration rate, loop diuretics.

Salt restriction is thought to be an important determinant of the efficacy of diuretic therapy in treatment of acute decompensated heart failure (ADHF). The 2010 Heart Failure Society of America guidelines on ADHF recommend sodium intake of <2 g/d and consideration of even greater salt restriction in patients with recurrent or refractory volume overload.[1] However, severe salt restriction causes a reduction in the glomerular filtration rate (GFR) because of decreased renal blood flow and an increase in tubular

reabsorption of sodium and water secondary to an increase in renin-angiotensin-aldosterone system (RAAS) activity.[2,3] In addition, salt restriction resets tubular glomerular feedback, which leads to reduction in GFR.[4] Salt restriction may have an antidiuretic and antinatriuretic effect.

On the other hand, loop diuretics are a cornerstone of fluid control and symptom relief in ADHF. Loop diuretics are associated with a classic dose-response curve between the rate of diuretic excretion and natriuresis. Patients with heart failure (HF) have a lower response to a given dose than normal subjects. Higher doses of diuretics are often used for greater severity of illness.[5] Because loop diuretics have a relatively short half-life and cause sodium reabsorption in tubules once the tubular concentration of the diuretics declines, administering high doses of diuretics multiple times per day is recommended to enhance effectiveness of the diuresis. However, loop diuretics may have harmful effects, including activation of RAAS and the sympathetic nervous system, electrolyte disturbances, and worsening of renal function (WRF) in a dose-dependent manner.[6] The observational study from the Acute Decompensated Heart Failure

National Registry (ADHERE) registry has shown associations among high doses of diuretics, in-hospital mortality, intensive care unit (ICU) stay, prolonged hospitalization, and WRF.[7]

A recent study reported that severe salt restriction may be invalid in patients hospitalized for ADHF.[8] Volpe et al (1997) demonstrated that salt intake reduces plasma renin activity and plasma aldosterone level and increases GFR despite increased salt intake being associated with sodium retention.[9] Thus, salt supplemented with low doses of diuretics should theoretically promote diuresis in patients with ADHF. However, there is little evidence to support this idea. In the present study, we tested the hypothesis that salt supplementation with low-dose furosemide would improve diuresis in patients hospitalized for ADHF.

Methods

Study Design

We conducted a prospective, randomized, open-label, controlled trial. The study was designed and conducted by the Division of Cardiovascular Medicine of Hyogo College of Medicine. The study was approved by the institutions' Ethical Committees, and every patient provided written informed consent before participating in the study.

Study Population

Patients with congestive HF were eligible if they were admitted to the Division of Cardiovascular Medicine of Hyogo College of Medicine from July 2011 to January 2012 for ADHF with symptoms of New York Heart Association functional class III/IV and had a systolic blood pressure of >80 mm Hg, estimated GFR (eGFR) of >15 mL min^{-1} 1.73 m^{-2}, and serum sodium level of <148 mmol/L. The exclusion criteria were use of inotropic agents, carperitide, hemodiafiltration, or noninvasive positive pressure ventilation (NPPV) and HF complicated by systemic infection, acute coronary syndrome, or distinct endocrine diseases (eg, syndrome of inappropriate secretion of antidiuretic hormone).

Forty-four patients were randomly assigned in a 1:1 ratio to (1) continuous intravenous infusion of 40 mg furosemide with 500 mL 1.7% sodium chloride solution per day or (2) continuous intravenous infusion of 40 mg furosemide with 500 mL 5% glucose solution per day.

Study Protocol

A stratified randomization scheme was used to assign the participants to the salt infusion or glucose infusion group. The stratification factors used in the randomization were sex and age. The study protocol is shown in Figure 1. The patients were administered either continuous intravenous infusion of 500 mL 1.7% NaCl supplemented with 40 mg/d furosemide (salt infusion group) or continuous intravenous infusion of 500 mL 5% glucose supplemented with 40 mg/d furosemide (glucose infusion group). For the patients who presented with acute pulmonary edema with hypertension (systolic blood pressure >160 mm Hg) and peripheral edema, nitroglycerin infusion was allowed until their blood pressure decreased to a normal level. Oral medications (digitalis, diuretics, β-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and aldosterone receptor antagonist) were continued throughout the study in all patients. Oral salt intake was restricted to 6 g/d and oral water intake to 500 mL/d in all patients.

All patients underwent physical examination for signs and symptoms of HF, measurement of supine blood pressure (BP) and heart rate (HR) at baseline and 24 hours after initiation of the treatment. In addition, multiple biomarkers, including plasma renin activity, plasma aldosterone, plasma norepinephrine, antidiuretic hormone, and N-terminal pro−B-type natriuretic peptide (NT-proBNP) for HF were measured. The equation refitted for Japanese individuals recently recommended by the Japanese Society of Nephrology was used to calculate the eGFR.[10] A bladder catheter was inserted for urine sampling. The total 24-hour urine volume was measured and urinalysis performed. Creatinine clearance (cCr) was calculated from plasma and 24-hour urinary creatinine [24-h urine creatinine concentration × 24-h urine volume]/[serum creatinine × 1,440 min/d]. The calculation was adjusted for body surface area. Chest radiography and echocardiography also were performed before the study and 24 hours after initiation of the study. The modified Simpson rule was used to determine the left ventricular ejection fraction. Transmitral inflow patterns were recorded from the left parasternal apical 4-chamber view. Early (E-wave) and late (A-wave) filling velocities and the E-wave deceleration time were measured. The modified Bernoulli equation was used to calculate the Doppler estimate of the systolic pressure gradient across the tricuspid valve.

Study End Points

Our primary end points were 24-hour urinary volume and improvement of dyspnea. The assessment of dyspnea improvement was made as described previously.[11] In brief; the patients were initially studied in the sitting position and first answered questions by choosing the best responses from a 5-point Likert scale. If the patients answered ''severely'' or ''very severely'' for being short of breath, they were not placed supine, to avoid worsening of their symptoms. Patients who were not severely or very severely short of breath underwent the orthopnea test (placed supine with head to horizontal). After an equilibration period of 120 seconds, the shortness of breath question was asked again and the answers again selected from a 5-point Likert scale. Patients with worse dyspnea and no change of score between baseline and 24 hours after initiation of the treatment were categorized as ''no dyspnea improvement,'' and those with improved dyspnea score were categorized as ''dyspnea improvement.'' The secondary end point was GFR estimated with 24-hour cCr.

Statistical Analysis

Values are expressed as mean ± SD if they fit normal distribution. Otherwise, values are expressed as median with interquartile range (IQR). The chi-square test was used to compare the nominal variables between the groups. Parameters that fit a normal distribution were analyzed with the use of paired/unpaired t tests. When the data did not fit a normal distribution, the Mann-Whitney/Wilson signed rank test was employed. A P value of $<.05$ was considered to indicate statistical significance. EZR (Saitama Medical Center, Jichi Medical University), a modified version of R commander (version 1.6-3) designed to add statistical functions frequently used in biostatistics, was used to perform all statistical analyses.[12]