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Hypertonic saline solution for prevention of renal dysfunction in patients with decompensated heart failure☆,☆☆

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ABSTRACT

Background: Renal dysfunction is associated with increased mortality in patients with decompensated heart failure. However, interventions targeted to prevention in this setting have been disappointing. We investigated the effects of hypertonic saline solution (HSS) for prevention of renal dysfunction in decompensated heart failure.

Methods: In a double-blind randomized trial, patients with decompensated heart failure were assigned to receive three-day course of 100 mL HSS (NaCl 7.5%) twice daily or placebo. Primary end point was an increase in serum creatinine of 0.3 mg/dL or more. Main secondary end point was change in biomarkers of renal function, including serum levels of creatinine, cystatin C, neutrophil gelatinase-associated lipocalin—NGAL and the urinary excretion of aquaporin 2 (AQP_2), urea transporter ($UT\text{-}A_1$), and sodium/hydrogen exchanger 3 (NHE_3).

Results: Twenty-two patients were assigned to HSS and 12 to placebo. Primary end point occurred in two (10%) patients in HSS group and six (50%) in placebo group (relative risk 0.3; 95% CI 0.09–0.98; $P = 0.01$). Relative to baseline, serum creatinine and cystatin C levels were lower in HSS as compared to placebo ($P = 0.004$ and 0.03, respectively). NGAL level was not statistically different between groups, however the urinary expression of AQP_2, $UT\text{-}A_1$ and NHE_3 was significantly higher in HSS than in placebo.

Conclusions: HSS administration attenuated heart failure-induced kidney dysfunction as indicated by improvement in both glomerular and tubular defects, a finding with important clinical implications. HSS modulated the expression of tubular proteins involved in regulation of water and electrolyte homeostasis.

1. Introduction

Heart failure is a condition associated with poor prognosis [1], and episodes of decompensation requiring hospital care are frequent [2]. In these circumstances, the occurrence of renal dysfunction carries a major prognostic burden [3] and even small changes in serum creatinine are associated with higher mortality rate [4]. Mechanisms involved in the simultaneous occurrence of cardiac and renal dysfunctions are scarcely understood, and therapies targeted to prevention of renal dysfunction in patients with decompensated heart failure have shown disappointing results [5,6].

In patients with heart failure, serum creatinine and estimations of glomerular filtration rate (GFR) are usually used to evaluate renal function. However, neither creatinine nor GFR completely represents the function of the kidney, which comprises glomerular function, tubular function, along with other specific metabolic and hormonal functions [7]. In this sense, markers other than creatinine are being used, such as cystatin C, which has been shown to be superior to serum creatinine in different patient populations [8], and neutrophil gelatinase-associated lipocalin (NGAL), an earlier marker of acute renal injury [9,10]. In addition, tubular cell transporters, such as aquaporin-2, can be detected in urine, and have been described as markers of tubular function in the setting of acute renal injury [11–13].

Hypertonic saline solutions have been studied in different forms of cardiovascular collapse since 1917 [14], and data from experimental shock models demonstrate that the infusion of 7.5% NaCl produces vasodilatation and increased regional blood flow to coronary [15], renal [16], intestinal and skeletal muscle [17] circulation. Additionally saline hypertonic improves renal function and myocardial contractility, a finding that is attributed to a direct cardiac inotropic effect induced by hypertonicity [18,19]. In patients, the infusion of 7.5% NaCl has been

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☆☆ Trial registration — NCT00555685 at www.clinicaltrials.org.

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successfully used in cardiogenic shock due to right ventricular infarction [20].

Small volumes of saline solutions have also been tested in patients with heart failure, [21,22] and most studies focused on safety and effectiveness aspects. A randomized trial reported as a secondary finding in a selective population of patients highly resistant to diuretics, that the infusion of saline solution with different tonicities was associated with lower creatinine levels [23]. However no previous study specifically examined the effects of saline solution over renal function in patients with decompensated heart failure, and mechanisms related to improved renal function in this setting remain unexplored.

Thus, we hypothesized that the infusion of hypertonic saline solution to patients with decompensated heart failure could prevent the occurrence of renal dysfunction. The aim of this study was to determine the effects of hypertonic saline solution on renal function in this setting, and study possible mechanisms. The primary outcome was increase in serum creatinine, and secondary outcomes included newer markers of both glomerular and tubular function, namely cystatin C, NGAL and tubular cell transporters.

2. Methods

2.1. Study design

The present study is a single-center, randomized, double-blind, placebo-controlled trial performed in a tertiary hospital dedicated to cardiology, and designed to evaluate the effects of the administration of hypertonic saline solution (NaCl 7.5%) to patients with decompensated heart failure for primary and secondary prevention for renal dysfunction. The study protocol was approved by the institutional Ethics Committee, and all patients gave written informed consent before enrollment. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [43].

Patients assigned to intervention group (HSS group) received a three-day course of 100 mL of hypertonic saline solution (NaCl 7.5%) infused during 1 h, twice daily. Patients assigned to placebo group received a three-day course of 100 mL of NaCl 0.9% infused during 1 h, twice daily. In both groups, the saline infusion was followed by an intravenous bolus dose of furosemide; the initial dose of furosemide was estimated considering the dose previously administered to patient, renal function and body weight; the initial dose could be modified along the course of the protocol, according to the initial patient response with the pre-established objective to achieve a weight loss of 500–1000 g per day.

2.2. Patients

Patients 18 years of age or older, admitted with the diagnosis of decompensated heart failure in the presence of congestive phenomena, with an ejection fraction of no more than 40% as measured by transthoracic echocardiography were considered eligible (Fig. 1). Patients were required to be receiving standard therapy for heart failure, as determined to be appropriate by their physicians, and according to current guidelines [24,25]. Criteria for the exclusion of patients were: patient refusal, signs of hypoperfusion, alcohol abuse, primary valvular disease, myocardial infarction or unstable angina within 6 months before randomization, cardiac surgery or angioplasty within 6 months before randomization, restrictive cardiomyopathy, chronic obstructive pulmonary disease, immunosuppressive therapy, malignant tumors, acute pulmonary embolism, surgical interventions or infections in the last 30 days, serum creatinine over 3.0 mg/dL, serum potassium over 5.5 mg/dL, any severe systemic disease expected to impair survival, pregnancy or childbearing potential. Intravenous inotropic therapy was not considered an exclusion criterion, but the dose of the inotrope was required to be unchanged for 48 h before randomization, in the absence of clinical parameters of hypoperfusion at the time of enrollment. In two patients, exclusion criteria occurred after randomization: one patient developed cardiogenic shock and another patient developed creatinine elevation up to 4.2 mg/dL after randomization but before intervention. The decision to exclude these patients was based on the fact that under these circumstances, the intervention was not safe to patients, and the occurrence of the primary outcome was compromised.

All eligible patients were recruited from June 2008 and August 2010 and were followed until December 2010.

2.3. Randomization and masking

For allocation of the participants, a computer-generated list of random numbers in blocks of three was used, in a proportion of two interventions to one placebo. Patients, investigators and care providers were blind to allocation; 7.5% NaCl and 0.9 NaCl solutions were identical in appearance, and prepared in bags consecutively identified by concealed codes, according to the randomization schedule. Randomization list was known exclusively by a pharmacist and a nurse not directly involved in the care of patients; they stored the randomization list, assigned patients to each group according to randomization schedule, and delivered the study medication. Investigators, patients and care providers were kept blind after assignment.

2.4. Outcome measures

The pre-specified primary outcome was an increase in serum creatinine of 0.3 mg/dL [4,6] or more during the study period, since this subtle creatinine elevation has been associated with higher mortality in the setting of acute decompensated heart failure.

Additionally, serum creatinine, urine output, body weight, serum sodium, urea, cystatin C, and neutrophil gelatinase-associated lipocalin (NGAL) were measured the day before the protocol was initiated, every day during the 3-day protocol, and 24 h after the end of the protocol. Markers of neurohumoral and inflammatory activation were measured before and after intervention. In order to further explore renal tubular function we measured the expression of renal tubular membrane proteins in urine (namely aquaporin 2 [AQP_2] sodium-hydrogen exchanger 3 [NHE_3] and urea transporter A1 [UTA_1]) before and after intervention. These transporters were selected because they are involved in mechanisms of urine concentrations, and also because they are present in different locations along the nephron.

Samples containing sera from patients were centrifuged and stored under −80 °C until analysis was performed with commercially available kits. Cystatin C and NGAL were determined in the serum of patients using enzyme linked immunosorbent assay (ELISA) kits (BioVendor LLC, North Carolina, USA); the limit of detection was

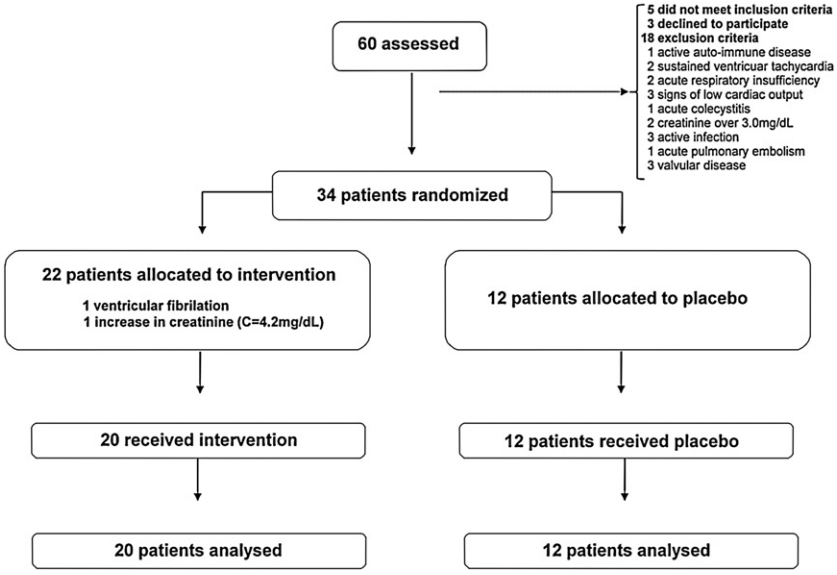

Fig. 1. Flow of participants through the trial.