Effects of Hypertonic Saline Solution on Body Weight and Serum Creatinine in Patients with Acute Decompensated Heart Failure

Responses to Reviewer #1 (00214259)

This is a well-written manuscript about the treatment of severe acute heart failure. Patients included in the trial are very sick and for many of them, this trial seems to be a last chance before switching to palliative care. Studies about this population are hard to do and that point needs to be considered in the decision to publish that manuscript. Also, almost all literature currently available on the matter comes from one Italian group and having insight about other groups is mandatory. Patients in the standard treatment group did not receive very high doses of diuretics. Do you believe that the better response observed with the treatment proposed could be only related to the increase of furosemide doses (independent of the saline infusion)?

We thank the reviewer for taking his time in reviewing our manuscript and rising positive comments on our work.

The mean daily dose of each strategy for furosemide administration during the standard treatment period was recalculated to exclude any 0 mg doses, an absent dose indicated an alternate route of delivery. Also, if a patient initiated treatment at day -3, missing values were excluded from preceding days (i.e. day -4). Such values had often been previously recorded as 0 mg received, in effect erroneously decreasing the mean and widening the standard deviation. Consequently, the mean daily dose of intravenous furosemide received in the standard treatment period was calculated to be 106±67 mg.

Nine patients received mainly oral furosemide during the standard treatment period, with a correspondingly larger mean daily dose of 196±165 mg. They did not receive a full course of intravenous furosemide as they already were prescribed chronic doses of oral furosemide. Moreover, they presented with acute kidney injury, oligo-anuria, and/or a degree of clinical instability that precluded an IV furosemide challenge and justified the immediate administration of hypertonic saline. Hypertonic saline was at times perceived as the last resource of treatment prior to realigning care towards palliative goals.

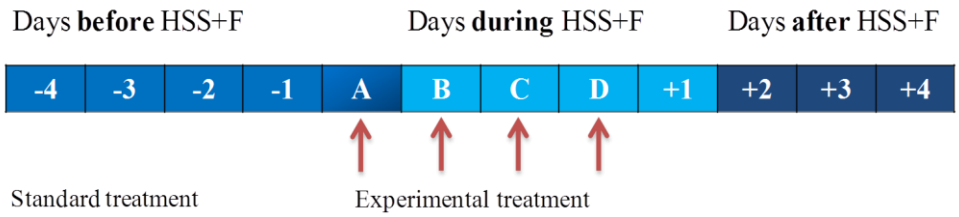
For our patients with worsening renal function, decreased urine output, and poor clinical response to escalating doses of diuretics, intravenous or high doses of oral furosemide were substituted by intravenous infusion of concomitant HSS+F. The apparent low mean daily dose of IV furosemide (106±67 mg) is attributed to the composition of our study population, where a significant proportion of patients were naive to loop diuretics, and did not present with heart failure at baseline (17%). Thus,

following a progressive titration of IV furosemide tailored to renal function and clinical response, most patients received a mean daily dose of 80 mg or more.

Substantial inter-patient variability reveals the need for further large-scale epidemiological investigation to define cohort characteristics stratified by "best-case" responders, namely patients in whom expansion of the effective intravascular volume with hypertonic saline improved glomerular filtration rate, thereby yielding greater load of filtered Na and delivery of diuretics into the urinary compartment; both effects contributing to improved diuretic response.

Some patients treated with low-dose IV diuretics responded poorly, even experiencing reduction in renal function; paradoxically, following treatment with high-dose furosemide andn hypertonic saline solution, clinical response improved and renal function was maintained. Only 5 patients (11%) had a significant deterioration in renal function (increase in serum creatinine of 27 µmol/L or more from Day A and Day +1, see Figure).

Data collection protocol and observation periods.



- first observation period: effects of the standard treatment on various parameters
- second observation period: effects of the experimental treatment (HSS+F) on various parameters

Of these patients, 2 died despite HSS+F administration, and 3 experienced a decrease in mean serum creatinine of 34 µmol/L by Day+4, with creatinine levels comparable to Day A. Several mechanisms explain the efficacy of the combination of HSS with intravenous furosemide for the treatment of advanced ADHF. By osmotic action HSS induces instantaneous mobilization of extravascular fluid into the intravascular compartment [1]. Increased plasma volume of up to 30% can be observed [2], serving a protective function against episodes of hypovolemia that are transiently or persistently present in patients with HF [3, 4], particularly when treated with IV diuretics; this volume expansion results in decreased peripheral vascular resistance via the baroreceptor reflex [5]. Thus, the increased preload, the decreased afterload and a possible inotropic effect induced by HSS [6, 7] facilitates an increase in the effective circulating volume which preserves renal blood flow and glomerular filtration rate intensive treatment with IV diuretics [8]. These mechanisms mitigate the massive

releases of renin and antidiuretic hormone that occur after days of treatment with IV loop diuretics. HSS can potentiate furosemide effects by transiently increasing Na serum concentration thereby allowing adequate inflow of this ion into the tubular lumen of the loop of Henle [9] concurrently as furosemide exerts its pharmacological action. Some studies [9, 10] have found concomitant administration of appropriate doses of HSS during treatment with IV diuretics may reduce diuretic resistance, referring to the systemic mechanism whereby reduced natriuretic response necessitates usage of greater doses of diuretics which in turn often results in deterioration of renal function [5].

Responses to Reviewer #2 (00211908)

There is one question raised after reading the well- written manuscript. Is there any data on cardiac biomarkers and NT Pro-BNP in this group of patients with acute decompensated heart failure.

We thank the reviewer for taking his time in reviewing our manuscript and rising positive comments on our work.

Brain natriuretic peptide (BNP) levels were collected in 33 (70%) patients prior treatment with HSS+F; remaining patients had single levels drawn only. The mean level of BNP was: 1685±1734 pg/mL on Day A or Day-1, prior to administration of HSS+F, and 1722±1589 pg/mL on Day C, D or +1. Increased BNP level after HSS+F administration was noted in 17 patients (52%). Paradoxically, in previous studies [9, 11], treatment of concomitant intravenous high-dose furosemide with HSS was significantly associated with a greater reduction in plasma levels of BNP when compared to non-HSS treatment, potentially attributed to the variable timing in BNP measurement. In these studies, BNP levels were measured on admission, prior to administering any treatment for heart failure, and at discharge or a few days post-treatment with HSS. Our protocol measured BNP levels at Day A, following standard administration of IV furosemide alone, and immediately following the last bolus of HSS+F. The hypertonic saline bolus mobilizes extravascular fluid into the intravascular compartment, transiently increasing plasma volume. Obtaining blood samples shortly after the last HSS+F bolus without allowing intercompartmental volume redistribution could falsely elevate BNP values. Interpretation of BNP results is further constrained by the small sample size of patients for whom BNP was measured before and after the experimental treatment, significant intragroup variations within BNP values, as well as the influence of the standard treatment on volume status.

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