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Original Article

Continuous infusion of furosemide versus intermittent boluses in acute decompensated heart failure: Effect on thoracic fluid content

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ABSTRACT

Introduction: The administration of loop diuretics in the management of acute decompensated heart failure (ADHF) whether IV boluses or continuous infusion is still controversial. We intended to evaluate differences between the two administration routes on the thoracic fluid content (TFC) and the renal functions.

Methods: Sixty patients with ADHF admitted to the critical care medicine department (Cairo University, Egypt) were initially enrolled in the study. Twenty patients were excluded due to EF > 40%, myocardial infarction within 30 days, and baseline serum creatinine level > 4.0 mg/dL. Furosemide (120 mg/day) was given to the remaining 40 pts who continued the study after 1:1 randomization to either continuous infusion (group-I, 20 pts) or three equal intermittent daily doses (group-II, 20 pts). Subsequent dose titration was allowed after 24 h, but not earlier, according to patient's response. No other diuretic medications were allowed. All patients were daily evaluated for NYHA class, urine output, TFC, body weight, serum K^+, and renal chemistry.

Results: The median age (Q1–Q3) was 54.5 (43.8–63.8) years old with 24 (60%) males. Apart from TFC which was significantly higher in group-I, the admission demographic, clinical, laboratory and co-morbid conditions were similar in both groups. There was statistically insignificant tendency for increased urine output during the 1st and 2nd days in group-I compared to group-II (p = .08). The body weight was decreased during the 1st day by 2 (1.5–2.5) kg in group-I compared to 1.5 (1–2) kg in group-II, (p = .03). These changes became insignificant during the 2nd day (p = .4). The decrease of TFC was significantly higher in group-I than in group-II [10 (6.3–14.5) vs 7 (3.3–9.8) $k\Omega^{-1}$ during the first day and 8 (6–11) vs 6 (3.3–8.5) $k\Omega^{-1}$ during the second day in groups-I&II respectively, P = .02 for both]. There was similar NYHA class improvement in both groups (p = .7). The serum creatinine was increased by 0.2 (0.1–0.5) vs 0 (−0.1 to 0.2) mg% and the CrCl was decreased by 7.4 (4.5–12.3) vs 3.1 (0.2–8.8) ml/min in groups-I&II respectively (p = .009 and .02 respectively).

Conclusions: We concluded that continuous furosemide infusion in ADHF might cause greater weight loss and more decrease in TFC with no symptomatic improvement and possibly with more nephrotoxic effect.

1. Introduction

Heart failure is a global public health burden, associated with high morbidity, mortality and cost. It occurs in 1–2% of adults in developed countries; this prevalence increase to about 8.4% in population above 70 years old.[1,2]

Diuretics, especially loop diuretics are commonly used in heart failure patients to alleviate symptoms of congestion, to improve exercise capacity,[3] and to reduce mortality risk.[4] The use of diuretics has however, many drawbacks. Rapid intravascular volume depletion and direct venodilation caused by diuresis may cause hypotension.[5] The use of loop diuretics is associated with activation of the renin-angiotensin-aldosterone and sympathetic nervous systems.[6,7] Furthermore, renal hypoperfusion induced by hypotension and the neuro-humoral activation may precipitate cardio-renal syndrome.[8,9] Hypokalemia is another commonly encountered complication that accompanies loop diuretics' administration.[10,11]

Intravenous loop diuretics are routinely administered either as intravenous boluses or continuous infusions. The most appropriate method of administration is still controversial. The use of

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continuous infusion may theoretically be more beneficial. Early studies showed that intravenous boluses are associated with paradoxical increase in systemic vascular resistance, increased neurohumoral activation and decreased cardiac indices.[9,12] The use of continuous infusion of loop diuretics was seen to increase diuretic efficacy and reduce diuretic toxicity by using lower doses in post cardiac surgery patients with heart failure.[13] On the other hand, the DOSE trial revealed no significant difference between continuous infusion and boluses in terms of efficacy and change from baseline renal functions.[14]

Impedance cardiography (IC) is a non-invasive method for continuous hemodynamic monitoring which is safe, reproducible and can be used across the wide spectrum of heart failure patients.[15] One of the valuable hemodynamic parameters that are assessed by IC is the thoracic fluid content (TFC). It is inversely related to the chest wall impedance-i.e.; as the TFC increases, chest wall impedance decreases-. TFC correlates with intravascular and extravascular fluid compartments in the chest.[16]

We intended in this study to compare intravenous furosemide administration as a continuous infusion versus intermittent boluses in patients with acute decompensated heart failure (ADHF) in terms of reducing TFC, clinical improvement and safety.

2. Patients and methods

This is a prospective, randomized, pilot study comparing continuous versus intermittent administration of intravenous furosemide in patients with a diagnosis of ADHF with evidence of volume overload. We included patients admitted to the critical care department, Cairo University Hospitals, Egypt in the period from November 2014 to July 2015 with volume overload. Volume overload was defined as: at least one symptom (dyspnea at rest, orthopnea or peripheral edema) plus at least one clinical sign (rales of pulmonary congestion, jugular vein dilatation, or a third heart sound).

We excluded from the study patients with an age of 18 years or less, patients with heart failure with preserved EF (EF > 40%), patients with recent myocardial infarction within 30 days of admission, patients with serum creatinine levels > 4.0 mg/dL and those who required renal replacement therapy during their hospital stay.

After enrollment, all patients were subjected to detailed history and clinical examination, emphasizing on the cause of heart failure, NYHA class, vital signs and urine output.

Complete blood count, liver function tests, cardiac biomarkers, serum creatinine, serum sodium and potassium were performed on admission and repeated daily for the 1st 3 days after admission. Creatinine clearance (CrCl) was estimated using the Cockcroft – Galt equation.[17]

All patients were randomized in a 1:1 ratio into two groups. Group I patients received furosemide infusion at a dose of 5 mg/h and Group II patients received furosemide at a dose of 40 mg every 8 h. Subsequent dose titration of furosemide was allowed only after 24 h of enrollment based on the patient's response.

The use of additional agents to manage ADHF (ACE-I/ARBs, Digoxin, Nitrates, Nor-adrenaline and/or Dobutamine) were decided based upon current guidelines of management of ADHF but no other types of diuretic agents were allowed during the study period.

Thoracic fluid content was measured using non-invasive electrical cardiometry device (ICON Cardiotronics, Inc, La Jolla, CA 92,307, Osypka Medical GmbH, Berlin, Germany). The device emits electrical current with high frequency-low constant amplitude that is interpreted by the device. This current is very low and is not harmful to patients. The measurement unit is $k\Omega^{-1}$. Normal value range is 25–35 $k\Omega^{-1}$.[18]

Electrical cardiometry was performed by applying 4 electrodes; 2 electrodes were applied to the neck on the left side (the 1st electrode placed above the root of the neck by about 5 cm and the 2nd electrode placed at the root of neck). The other 2 electrodes were applied to chest wall (one was placed on the level of xiphoid on the left side and the other placed 5 cm lateral to the previously placed electrode at level of anterior axillary line). Patient data including gender, weight, height and age were fed to the device before obtaining measurements. TFC was measured on admission and then 24 h and 48 h later. The decrease in TFC over time was estimated as Δ TFC. Δ TFC_1 represents the decrease during first 24 h (Δ TFC_1 = TFC on admission – TFC after 24 h) and Δ TFC_2 represents the decrease during the second day of admission (ΔTFC_2 = TFC after 24 h – TFC after 48 h).

All patients were monitored for hourly urine output for every kg of body weight (mL/kg/h) and weight reduction (weight reduction during 1st 24 h = body weight on admission – body weight after 24 h) (kg/day). The evaluated adverse effects included serum electrolytes, renal functions and occurrence of acute kidney injury (defined as acute elevation of serum creatinine $\geq$0.3 mg/dl within 48 h).[19] Occurrence of hypokalemia (defined as serum K^+ level $\leq$ 3.5 meq/L) and the need of vasoactive and/or inotropic support were evaluated.

Other outcome parameters evaluated included average ICU length of stay (ICU-LOS) and in-hospital mortality.

Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review board at Cairo University.

2.2. Statistical methods

Data were prospectively collected and coded prior to analysis using the statistical package of social science (SPSS version 16). Normal distribution of different dependent variables in relation to their independent variables was studied. A variable was considered normally distributed if the Shapiro-Wilk's test had a P > .05.[20,21] and with z-value of skewness and kurtosis between −1.96 and +1.96.[22] Most of our variables were non-normally distributed and accordingly all continuous variables were expressed as median (25th percentile-75th percentile). Categorical variables were expressed as frequency and proportion.

Nonparametric Mann-Whitney U test was used for comparison between two groups as regard quantitative variable and Wilcoxon test was used for paired comparisons for TFC on admission and after 24 h. Chi-Square Test (x^2) was used for comparison between two groups about qualitative data. Exact test was used instead when the expected frequency is less than 5. P value $\leq$ 0.05 was considered statistically significant.

3. Results

A total of 60 patients were initially enrolled in the study. 11 patients were excluded for preserved ejection fraction (>40%), 4 for serum Creatinine > 4 mg/dL, and 5 for recent myocardial infarction within 30 days of admission. Thus, 40 patients (24 males and 16 females) with a median age (Q1–Q3) of 54.5 (43.8–63.8) years old were randomly assigned to one of the two groups; Group I (n = 20 patients) representing those who received furosemide in the form of continuous IV infusion and Group II (n = 20 patients) representing those who received furosemide in three daily intermittent boluses. The baseline demographic and clinical criteria of the patients' population are presented in Table 1.

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