International Journal of Cardiology 174 (2014) 516–523

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Antigen carbohydrate 125 and creatinine on admission for prediction of renal function response following loop diuretic administration in acute heart failure

Julio Núñez [a,*,1], Pau Llàcer [b,1], Eduardo Núñez [c,1], Silvia Ventura [d,1], Clara Bonanad [d,1], Vicent Bodí [a,1], Gema Miñana [e,1], Enrique Santas [d,1], Beatriz Mascarell [d,1], Gregg C. Fonarow [f,1], Francisco J. Chorro [a,1], Juan Sanchis [a,1]

[a] Servicio de Cardiología, Hospital Clínico Universitario, INCLIVA, Universitat de Valencia, Spain
[b] Servicio de Medicina Interna, Hospital de Manises, Valencia, Spain
[c] Servicio de Cardiología, Hospital Clínico Universitario, INCLIVA, Spain
[d] Servicio de Cardiología, Hospital Clínico Universitario, Spain
[e] Servicio de Cardiología, Hospital de Manises, Valencia, Spain
[f] UCLA Division of Cardiology, Ahmanson-UCLA Cardiomyopathy Center, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 30 January 2014
Received in revised form 31 March 2014
Accepted 9 April 2014
Available online 18 April 2014

Keywords:
Antigen carbohydrate 125
Loop diuretics
Renal Failure
Acute heart failure

ABSTRACT

Background: The use of loop diuretics in acute heart failure (AHF) is largely empirical and has been associated with renal function impairment by reducing renal perfusion but also renal improvement by decreasing renal venous congestion. Antigen carbohydrate 125 (CA125) has emerged as a proxy for fluid overload. We sought to evaluate whether the early changes in creatinine (ΔCr) induced by intravenous furosemide doses (ivFD) differ among clinical groups defined by overload status (CA125) and creatinine on admission (Cr).

Methods and results: We included 526 consecutive patients admitted for AHF. All patients received intravenous furosemide for the first 48 hours. CA125 and Cr were dichotomized at 35 U/ml and 1.4 mg/dl, respectively, and grouped as follows: C1 [Cr <1.4, CA125 ≤35 (n = 151)]; C2 [Cr <1.4, CA125 >35 (n = 241)]; C3 [Cr ≥1.4, CA125 ≤35 (n = 45)]; and C4 [Cr ≥1.4, CA125 >35 (n = 89)]. Clinicians in charge of the management of patients were blind to CA125 values. ΔCr was estimated as the absolute difference in Cr between admission and 48–72 hours. Multivariable linear regression analysis was used for modeling purposes. The adjusted analysis showed a differential effect of ivFD on ΔCr. Per increase in 20 mg/day of ivFD, the mean ΔCr was 0.010 mg/dl (p = 0.464) in C1, 0.002 mg/dl (p = 0.831) in C2, 0.045 mg/dl (p = 0.032) in C3, and −0.045 mg/dl (p < 0.001) in C4 (omnibus p < 0.001). A similar pattern of response was observed in a validation cohort.

Conclusions: In patients with AHF, the magnitude and direction of ΔCr attributable to ivFD were differentially associated with values of CA125 and Cr on admission.

1. Introduction

Administration of intravenous loop diuretics (LDs) constitutes the mainstay therapy for treatment of fluid overload in patients with acute heart failure (AHF); however, their use is largely empirical, and mainly guided by the severity of symptoms and signs that have revealed a limited ability to quantify the degree of fluid overload. Not infrequently, LDs, particularly at higher doses, are associated with important deleterious effects such as worsening renal function (WRF) and increased mortality among others [1–4]; however, it is unclear why a subset of patients either do not develop WRF or even improve its renal function in response to the administration of LDs. In fact, recent publications have suggested that this double edge-sword effect of LDs on renal function is largely determined by a delicate balance between renal perfusion and venous congestion. On the harmful side, the administration of LDs may lead to intravascular volume depletion, reduced renal perfusion and deterioration in renal function. On the beneficial side, glomerular filtration rate can improve with LDs, by decreasing venous congestion [5–8].

There is yet no consensus about what is the best proxy for fluid overload in AHF [9,10]. Classical symptoms, signs, chest radiography,

* Corresponding author at: Servicio de Cardiología. Hospital Clínico Universitario, Avda. Blasco Ibáñez 17. 46010 Valencia-España. Tel.: +34 652856689; fax: +34 963862658.
E-mail address: yulnunez@gmail.com (J. Núñez).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2014.04.113
0167-5273/

biomarkers (such as natriuretic peptides), echo parameters, and even invasive measurement of pulmonary and central venous pressures have shown limited discriminative ability in this respect [9,10]. Contemporary evidence suggests a potential role for the antigen carbohydrate 125 (CA125) as a surrogate for fluid overload. CA125 has correlated with clinical, hemodynamic and echocardiographic parameters indicative of disease's severity and with signs and symptoms of congestion [11–13]. In addition, higher levels of CA125 have shown to be independently associated to mortality and/or subsequent admission for AHF [11–13]. The wide availability, low cost and close correlation between CA125 changes and disease severity and clinical outcomes make this marker a potential tool for guiding therapy in AHF [12,14,15].

In addition, the presence of renal dysfunction on admission has shown to be either an important risk factor for developing WRF during hospitalization [1,16] or an indicator for an already developed (preadmission) WRF, a situation where an improvement in renal function may also occur [17].

Following these previous postulates, we hypothesize that, in patients with AHF, the net effect of the administration of LDs on renal changes (and its clinical implications in terms of short-term hospital readmission and/or mortality) largely depends on: a) renal function status on admission, and b) degree of fluid overload. As such, our goal was to determine whether early renal changes (48–72 hours after admission) are determined by the intravenous furosemide doses (ivFD), and whether this effect is differentially modified by baseline plasma levels of CA125 and creatinine (Cr). As a secondary endpoint, we sought to evaluate the relationship between ivFD and the 60-day risk of death/readmission, and whether this effect varies within the groups defined by CA125 and Cr.

2. Methods

2.1. Study group and protocol

We studied a consecutive cohort of 526 patients admitted for AHF in the cardiology department of a third-level center (Hospital Clínico Universitario de Valencia) from 1st July 2010 to 1st July 2012. AHF was defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function and the presence of objective evidence of structural or functional abnormality of the heart at rest (cardiomegaly, third heart sound, cardiac murmur, abnormality of the echocardiogram or raised natriuretic peptides) [18]. Patients with a final diagnosis of pneumonia, sepsis, acute coronary syndrome or end-stage renal failure on dialysis or imminent need of dialysis were excluded from this study. Demographic data, medical history, vital signs, 12-lead electrocardiogram, laboratory data and treatments were routinely determined during hospitalization following pre-established registry questionnaires. Left ventricular ejection fraction (LVEF) was assessed by echocardiography (Agilent Sonos 5500-Phillips) during index hospitalization. All patients received intravenous furosemide for the first 48 hours. Treatment with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, aldosterone antagonists, anticoagulants and other therapeutic strategies were individualized following established guidelines [18]. The protocol was approved by the ethical committee of our center and all subjects gave written informed consent to participate in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee [19].

Three main interacting players were considered: 1) admission renal function status, 2) CA125 levels, and 3) the average ivFD administered during the first 48 hours.

1) Renal function status on admission: Renal failure (RF) was defined as serum creatinine ≥1.4 mg/dl [19].
2) CA125 levels: Using a commercially available immunoassay (Elecsys CA125 II assay-Roche Diagnostics), CA125 was measured during the first 12 hours of admission in all cases, and dichotomized into two groups according to a cut point recommended by this reactive manufacturer: normal CA125 (≤35 U/ml) and high CA125 (>35 U/ml). Using these two binary markers (Cr ≥1.4 mg/dl and CA125 >35 U/ml), a composite variable with 4 levels was created: C1 = Cr <1.4 and CA125 ≤35; C2 = Cr <1.4 and CA125 >35; C3 = Cr ≥1.4 and CA125 ≤35; and C4 = Cr ≥1.4 and CA125 >35. This composite variable reflects an attempt to characterize different pathophysiological groups based on renal function and fluid overload status: C1 (normal-to-mild RF/mild fluid overload); C2 (normal-to-mild RF/moderate-severe fluid overload); C3 (moderate-to-severe RF/mild fluid overload); and, C4 (moderate-to-severe RF/moderate-severe fluid overload).
3) Intravenous loop diuretics: All patients received intravenous furosemide on admission (for at least the first 48 hours). The diuretic dose titration was left at discretion of the health-care professional but blind to CA125 values. Thus, the average daily dose used within the first 48 hours was calculated. Furosemide was administered in bolus unless the doses were higher than 250 mg/day, in which case it was administered as a continuous infusion. For description (Table 1), ivFD were divided into three categories: <80, 80–120, and >120 mg/day.

2.2. Endpoints

The main endpoint was to determine the effect of ivFD on changes in Cr between admission and 48–72 hours (ΔCr). Other surrogates of renal function, such as changes in urea (ΔUrea) and percentage changes in estimated glomerular filtration rate (Δ%GFR) were also evaluated. GFR was estimated from the 4-variable Modification of Diet in Renal Disease study equation. The secondary endpoint was to determine the prognostic effect of the ivFD doses on the composite of 60-day mortality/unplanned readmission risk according to C1–C4 groups.

2.3. Statistical analysis

Continuous variables were expressed as mean ± 1 standard deviation (SD) or median (IQR) when appropriate. For their comparison between the 3 ivFD groups (<80, 80–120, and >120 mg/day), ANOVA or Kruskal-Wallis rank test was used as appropriate. Discrete variables were presented as percentages and compared with Chi^2 test.

Two modeling strategies were used for hypothesis testing: multivariable linear regression analysis, and survival analysis.

2.3.1. Multivariable linear regression analysis

For this model, ΔCr had a role of dependent variable. In two sensitivity analyses, ΔUrea and Δ%GFR were also modeled. The exposure consisted of a triple interaction between C1–C4 categories and ivFD (continuous). Variables selection was performed by backward elimination using a multivariable fractional polynomial (FP) algorithm [20]. The best fitted model was selected based on the Akaike information criterion (AIC). This included the best set of covariates and the best fractional polynomials for continuous variables that did not meet the linearity assumption. Estimates are presented as β-coefficients with their respective 95% CIs.

The generalizability of these estimates was also tested by developing a similar regression model in an external cohort (validation dataset) of 202 consecutive patients admitted for AHF from 1st June 2010 to 16th January 2013 in the Internal Medicine Department of Hospital de Manises (Valencia-Spain).

2.3.2. Survival analysis

The event rates of mortality/readmission were estimated among categories of ivFD, assuming an exponential distribution. For multivariable regression, a parametric version of Cox proportional hazard was used [21]. For this model, candidate covariates were chosen based on previous medical knowledge and independent of their p-value. Then, a reduced and parsimonious model was derived by using backward stepwise selection with a p-value of 0.157 for variable inclusion. During this selection process, the linearity assumption for all continuous variables was simultaneously tested and transformed, if appropriate, with fractional polynomials or restricted cubic splines [20]. The proportionality assumption for the hazard function over time was tested by the Schoenfeld residuals. The model's discriminative ability was assessed by the C-statistics.

A 2-sided p-value of <0.05 was considered to be statistically significant for all analyses. All analyses were performed using Stata 12.1 [StataCorp. 2011. Stata Statistical Software: Release 12. College].

3. Results

3.1. Baseline characteristics of the population

The mean age was 73.1 ± 11.4 years and 48.5% were males. The distribution of the population [N (%)] according to C1 to C4 categories were: C1 = 151 (28.7%), C2 = 241 (45.8%), C3 = 45 (8.6%), and C4 = 89 (16.9%). The mean ± SD of ivFD (mg/day) administered increased monotonically from C1 to C4: C1 = 79 ± 32.1, C2 = 85 ± 39.8, C3 = 89 ± 38.2, and C4 = 102 ± 49.8, $p < 0.001$.

3.2. Differences in baseline characteristics among categories of ivFD (Table 1)

Patients with hypertension, coronary heart disease, previous NYHA III–IV, higher Charlson index, pleural effusion, peripheral edema and prior treatment with oral furosemide and beta-blockers were more frequently treated with higher ivFD. Likewise, a positive (and significant) association among ivFD groups and red cell distribution width, Cr, urea, NT-pro brain natriuretic peptide (NT-proBNP), CA125, and gamma-glutamil transpeptidase was also documented. Conversely, patients in whom the index admission corresponded to their first admission were