Predisposing Factors for Acute Kidney Injury in Hispanic Patients Treated with Diuretics for Decompensated Heart Failure

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Objective: In patients with congestive heart failure (CHF), use of loop diuretic therapy may result in acute kidney insufficiency (AKI). We assessed the factors that contributed to the development of AKI in patients with CHF treated with loop diuretics in a sample of patients who attended the Cardiovascular Center of Puerto Rico and the Caribbean (CCPRC).

Methods: Medical records of 236 patients admitted between: January 1, 2008 to December 31, 2008 with the diagnosis of CHF were reviewed. Diagnosis of CHF based on symptoms and signs was confirmed by echocardiography. Twenty six (26) patients with significant valvular disease and four (4) patients who did not receive diuretics during hospitalization were excluded. Hospital course was observed until diuretic therapy was discontinued or patient was discharged. AKI was defined as a 25% increase in serum creatinine level after the start of diuretic therapy. The study sample was categorized in two groups: patients who developed AKI and those who did not. Variables associated with AKI ($p<0.05$) in the bivariate logistic regression models were included in the multivariate logistic regression models.

Results: In the multivariate logistic regression model, only a greater dose of diuretic therapy (>80 mg/dl) and history of diabetes mellitus were significantly ($p<0.05$) associated with AKI.

Conclusion: Analysis of data shows that increased doses of diuretic therapy and history of diabetes mellitus were significantly associated with AKI in patients with CHF. This study highlights the importance of monitoring the doses of diuretic therapy during hospitalization, in this group of patients. [*P R Health Sci J 2013;2:63-67*]

Key words: Acute Kidney Injury (AKI), Congestive Heart Failure (CHF), Diuretics

The pathophysiology of congestive heart failure (CHF), one of the leading causes of death worldwide, is characterized by the activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), producing sodium and water retention (1, 2). It is well accepted that the therapeutic approach of decompensated CHF includes the use of intravenous loop diuretics to decrease sodium and water retention. However, diuretic therapy in these individuals may result in further activation of the RAAS and SNS, impairing renal blood flow (RBF) and glomerular filtration rate (GFR), causing diminished kidney function, which may lead to acute kidney injury (AKI) (3, 4). Hospital associated AKI is a common entity which may affect 15% of hospitalized patients (5). Development of AKI and increased mortality have been associated with high doses of loop diuretics during hospitalizations (6). In addition, other factors as the use of angiotensin converting enzyme inhibitors (ACEI), volume depletion, and non-steroidal anti-inflammatory agents have also been identified as risk factors for the development of AKI after treatment with loop diuretics in CHF (7).

In view of the importance of this therapeutic modality producing harmful effects that may increase morbidity and mortality, we analyzed our experience in the Cardiovascular Center of Puerto Rico and the Caribbean (CCPRC) with the use of loop diuretics in patients with CHF to identify the factors that may contribute to the development of AKI in our Hispanic population.

Methods

Medical records of 236 patients admitted to the CCVPRC between January 1st, 2008 and December 31, 2008 with the

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diagnosis of decompensated CHF (ICD-9 code 428) were reviewed. Only patients with a clinical diagnosis of congestive heart failure based on symptoms (fatigue, dyspnea, orthopnea) and physical signs (elevated jugular venous pressure, chest rales, S3 gallop, or edema) and confirmed by echocardiography that received furosemide during hospitalization were included. Twenty six patients with significant valvular disease (severe aortic stenosis and severe mitral stenosis) were excluded because they underwent valve replacement surgery during admission. Four patients were also excluded because they did not receive diuretic therapy during hospitalization. The hospital course of 206 patients was examined until diuretic therapy was discontinued or patients were discharged. Transthoracic Echocardiography (TTE) was performed on all patients. Left Ventricular Systolic Dysfunction (LVSD) was defined as an Ejection Fraction (EF) less than 50% and Left Ventricular Diastolic Dysfunction (LVDD) was defined as an EF greater than 50% in the presence of left ventricular hypertrophy with an abnormal mitral inflow pattern. Meanwhile, AKI was defined as 25% increase in serum creatinine after the initiation of diuretic therapy. Patients were categorized into those who developed renal insufficiency and those who did not. The study procedures were reviewed and approved by the Institutional Review Board (IRB) of the University of Puerto Rico Medical Sciences Campus.

The data collection instruments included demographic information (age and gender), and clinical information [presence of chronic kidney disease (CKD) defined by previous history and baseline creatinine levels, type of cardiac dysfunction (systolic vs diastolic), history of diabetes mellitus (DM), clinical laboratory data including Blood Urea Nitrogen (BUN), serum creatinine before and after diuretic therapy, dose and duration of furosemide, use of other therapeutic agents administered for the treatment of CHF such as ACEI, angiotensin receptor blockers (ARB's), digitalis, β adrenergic blockers, calcium channel blockers, and spironolactone].

Statistical analysis

Chi-square statistics was used to compare the distribution of demographic and clinical characteristics across AKI status. Generalized equations were fitted to estimate risk ratio (RR) with 95% confidence intervals (CI) for AKI. Variables significantly associated with AKI ($p<0.05$) in the bivariate logistic regression model were included in the multivariate logistic regression model using Stata for Windows release 10.0 (Stata Corporation, College Station, Texas).

Results

Table 1 shows the demographic characteristics and baseline clinical data for our population sample. Of 206 patients, 115 (56%) were older than 60 years and more than a half were males (60%). Systolic dysfunction (86%) was found the more common type of CHF in the population sample compared to diastolic dysfunction (14%). A total of 63 (30%) patients were overweight and 109 (52%) were obese. Arterial hypertension was documented in 167 (81%) and DM in 121 (58%) of patients. History of CKD was observed only in 68 (33%) of patients.

Table 1. Demographics and baseline clinical data for the study sample (n=206)

Characteristics	N (%)
Age (years)	
< 60	91 (44.17)
≥ 60	115(55.83)
Gender	
Male	124 (60.19)
Female	82 (39.81)
*Type of CHF**	
Systolic	178 (86.41)
Diastolic	28 (13.59)
BMI† (kg/m²)	
Underweight/Normal (0-24.9 kg/m²)	34 (16.50)
Overweight (25.0-29.9 kg/m²)	63 (30.58)
Obesity (≥30.0 kg/m²)	109 (52.91)
Arterial Hypertension	
Yes	167 (81.07)
No	39 (18.93)
Diabetes Mellitus	
Yes	121 (58.74)
No	85 (41.26)
Previous history of CKD‡	
Yes	68 (33.01)
No	138 (66.99)

*Congestive Heart Failure; †Body Mass Index; ‡Chronic Kidney Disease

Table 2 describes the clinical characteristics in patients with or without AKI. Of the 206 patients studied, 77 (37.4%) developed AKI and 72 patients (93.5%) of AKI group, had systolic dysfunction. Our study sample does not differ by age or sex ($p < 0.05$). However the proportion of patients with DM (76.62%) and history of CKD (57.14%) was significantly higher in the AKI group ($p <0.05$). Systolic heart failure was also significantly higher (93.5%) in patients with AKI ($p < 0.05$). A baseline of BUN of more than 30 mg/dL (67.53%) and a baseline creatinine of more than 1 mg/dL (87.01%) were also seen in this group. An association between furosemide doses of more than 80 mg/day and development of AKI (79.22%) was statistically significant ($p<0.05$).

Table 3 shows the estimation of the unadjusted and adjusted RR for participants with AKI. The bivariate-unadjusted model showed that systolic CHF, history of CKD, dose of diuretic therapy, baseline creatinine and BUN, history of DM, and concurrent use of spironolactone were significantly ($p <0.05$)

associated with AKI. However, the multivariate-adjusted model showed that only the presence of DM (RR= 2.28, 95% CI: 1.02-5.10) and increasing doses of diuretics (RR= 1.05, 95% CI: 1.03-1.08) remained significantly (p< 0.05) associated to AKI.

Figure 1 demonstrates that a higher daily furosemide dosage (>80 mg/day) significantly increases the risk of developing AKI.

Table 2. Baseline clinical characteristics in patients by AKI† status (n=206)

Characteristics	AKI (n=77) N (%)	No AKI (n=129) N (%)	P-value*
Age (years)			0.56
< 60	32 (41.56)	59 (45.74)	
≥ 60	45(58.44)	70(54.26)	
Gender			0.17
Male	51 (66.23)	73 (56.59)	
Female	26 (33.77)	56 (43.41)	
Type of Heart Failure			<0.05
Systolic	72 (93.51)	106 (82.17)	
Diastolic	5 (6.49)	23 (17.83)	
Diabetes Mellitus			<0.05
Yes	59 (76.62)	67 (51.94)	
No	18 (23.38)	62 (48.06)	
Previous history of CKD‡			<0.05
Yes	44 (57.14)	24 (18.60)	
No	33 (42.86)	105 (81.40)	
*Baseline BUN** (mg/dL)*			<0.05
≤ 30	25 (32.47)	97 (75.19)	
> 30	52 (67.53)	32 (24.81)	
Baseline Cr§ (mg/dL)			<0.05
< 1	10 (12.99)	56 (43.41)	
≥ 1	67 (87.01)	73 (56.59)	
Furosemide dose (mg/day)			<0.05
≤ 80	16 (20.78)	88 (68.22)	
> 80	61 (79.22)	41 (31.78)	
Furosemide duration (days)			<0.05
≤ 5	39 (50.65)	85 (65.89)	
> 5	38 (49.35)	44 (34.11)	
Spironolactone			<0.05
Yes	16 (57.10)	12 (42.90)	
No	24 (37.4)	50 (67.6)	

*P-values from chi-square distribution; †Acute Kidney Injury; ‡Chronic Kidney Disease; **Blood Urea Nitrogen; §Creatinine

Discussion

To our knowledge, this is the first epidemiological study to assess the predisposing factors for AKI among a Hispanic clinical-based sample of patients treated with diuretics for decompensated heart failure in Puerto Rico. Our data showed an increased risk of developing AKI in the presence of DM and increasing doses of loop diuretics. Although not significant in the adjusted-multivariate analysis, the unadjusted-bivariate model showed that history of CKD, length of diuretic therapy, increased baseline creatinine and BUN level, left ventricular systolic dysfunction, and concurrent use of spironolactone were associated with AKI.

Table 3. Analysis of predictors of AKI* among patients with CHF† receiving diuretic therapy

Characteristic	Unadjusted RR (95% CI)	AdjustedRR (95% CI)
Age (years)	1.01 (0.99-1.03)	1.00 (0.98-1.03)
Sex		
Female	1.0	1.0
Male	1.50 (0.84-2.71)	1.33 (0.60-2.95)
Type of CHF†		
Diastolic	1.0	1.0
Systolic	3.12 (1.14-8.60)	2.55 (0.64-10.12)
Previous history of CKD‡		
No	1.0	1.0
Yes	5.83 (3.10-10.98)	2.37 (0.78-7.22)
Furosemide dose (mg/day)	1.05 (1.04-1.07)	1.05 (1.03-1.08)
Duration of furosemide (days)	1.07 (1.00-1.14)	1.04 (0.95-1.14)
Baseline Creatinine (mg/dL)	4.36 (2.25-8.44)	1.84 (0.73-4.63)
*Baseline BUN** (mg/dL)*	1.02 (1.01-1.04)	1.01 (0.99-1.03)
Spironolactone use	1.99 (1.09-3.62)	0.79 (0.34-1.84)
Diabetes Mellitus		
No	1.0	1.0
Yes	3.54 (1.89-6.66)	2.28 (1.02-5.10)

*Acute Kidney Injury; †Congestive Heart Failure; ‡Chronic Kidney Disease; **Blood Urea Nitrogen

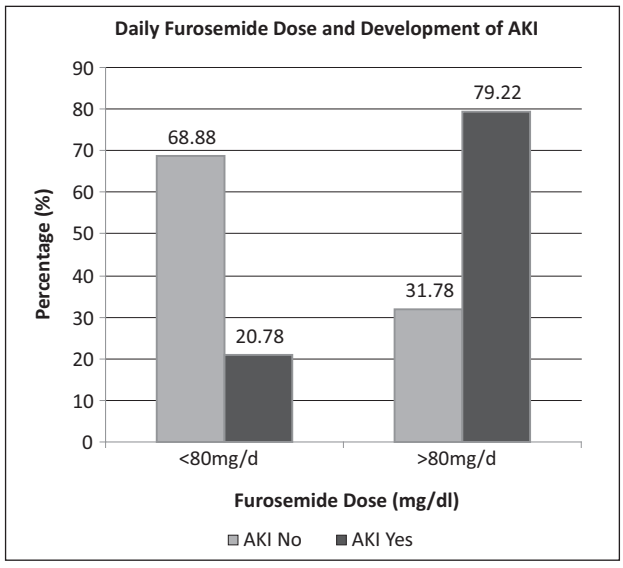

Figure 1. Daily Furosemide Dose and Development of AKI

In this study, the presence of DM was a major risk factor for the development of AKI. Similarly, in a large cohort study, history of DM was a significant predictor of in-hospital renal dysfunction among patients with congestive heart failure (8). The mechanism by which DM aggravates the kidney function in these patients is not altogether clear. It is possible that the presence of nephropathy, endothelial dysfunction or dehydration (in patients with uncontrolled blood sugar) may serve as a precipitating factor.

Loop diuretics might protect the kidneys against ischemic injury (9). They may inhibit sodium transport in the ascending loop of Henle, increase renal blood flow, reduce renal tubule oxygen consumption and might hasten recovery of AKI by washing out tubular debris. Based on this, loop diuretics might be expected to prevent or ameliorate AKI. Notwithstanding, studies have been performed to ascertain whether loop diuretics, specifically furosemide are beneficial in the prevention or treatment of AKI. However, there is no evidence that the use of diuretics reduces the incidence or severity of AKI. Use of furosemide proved to be harmful after cardiac sugery (10) and when given for contrast induced AKI (11).

On the other hand, the effect of loop diuretics in patients with CHF has been extensively studied. High doses of loop diuretics have been associated to decreasing renal function (12, 13). In contrast, several small studies have suggested that continuous infusion as compared to bolus administration, is associated with a lesser degree of renal dysfunction and greater diuresis. A recent prospective, double blind, randomized study (14) in 308 patients with acute decompensated CHF compared the use of a bolus of furosemide every 12 hours and continuous infusion in both high and low dosages. In this study, there was no significant difference in patient's global assessment of symptoms or in the change of renal function when diuretic therapy was administered by bolus or with continuous infusion in high or low doses. However, the high dose strategy was associated with greater diuresis and more favorable outcomes in some secondary endpoints, but also with transient worsening of renal function. These findings are in accordance with the retrospective analysis in our Hispanic population which showed a statistically significant association between the development of AKI and increased doses of furosemide, despite the fact that patients were not classified based on diuretic route of administration (bolus vs infusion).

The importance of avoiding the development of AKI relies in that it has been linked with an increased risk of developing CKD at long term. A meta-analysis of thirteen cohort studies revealed that patients with AKI had higher risk for developing CKD and death compared to patients without AKI (15), proposing it as an independent risk factor for CKD, End Stage Renal Disease (ESRD) and death. Similarly a large study including an analysis of 30,207 hospital discharged patients demonstrated that 1,610 of these patients experienced AKI (16). Upon matching to 3,652 control patients without AKI, it was found that an increased number of patients with AKI developed CKD during longitudinal follow up. Those who developed CKD after resolving AKI, had a substantial increase in mortality risk. Furthermore, a multicenter observational study of 9,425 patients who survived to hospital discharge after major surgery showed that patients with AKI-on-CKD during hospitalization had significantly worse long-term survival on a median follow up of 4.8 years than patients with AKI, but without CKD (17). These studies confirm the importance of developing management strategies to prevent AKI in hospitalized patients.

There are some important limitations to our study. First, this was a retrospective analysis. Second, we lack evidence of previous episodes of CHF and use of diuretics in our population, which may have affected renal function. Finally, there was no follow up after hospital discharge. The fact that DM is an additive risk factor for AKI in these patients may point to a greater degree of cardiovascular disease in this group of diabetic patients.

In conclusion, our study supports the notion that increased doses of diuretics may affect renal function in patients with CHF and that the presence of DM may be an additive risk factor for AKI. In view of the recent studies showing the association of AKI and development of CKD and increased mortality, it is recommended that in our Hispanic population, increasing doses of furosemide should be avoided or used with extreme caution, especially in diabetic patients with decompensated heart failure. Additional prospective studies are necessary to better define risk factors that may predispose congestive heart failure patients to develop AKI.

Resumen

Objetivo: El uso de diuréticos en pacientes con fallo cardiaco puede resultar en un insulto renal agudo (ARI). Se evaluaron los factores que pudiesen contribuir al desarrollo de ARI en una muestra de pacientes del Centro Cardiovascular de Puerto Rico y del Caribe con un diagnóstico de fallo cardiaco agudo, tratados con diuréticos del asa de Henle. Métodos: Se revisaron 236 expedientes desde el 1 de enero hasta diciembre 31 del 2008 con un diagnóstico de fallo cardiaco agudo confirmado por ecocardiografía transtorácica. Veintiséis (26) pacientes con enfermedad valvular severa y cuatro (4) pacientes que no recibieron diuréticos durante la hospitalización fueron excluidos. El curso hospitalario se revisó hasta que el paciente fue dado de alta o hasta que se descontinuaran los diuréticos. ARI fue definido como un aumento de 25% en el nivel de creatinina sérica luego de comenzar la terapia con diuréticos. La muestra del estudio se categorizó en dos grupos: pacientes que desarrollaron y no desarrollaron ARI. Las variables asociadas al desarrollo de ARI en el análisis bivariado fueron incluídas en el modelo de regresión logística multivariado. Resultados: El modelo de regresión logística multivariada demostró que un aumento en la

dosis de diuréticos (>80 mg/dL) e historial de diabetes mellitus estuvieron asociados al desarrollo de ARI (p<0.05). Conclusión: Este estudio muestra que mayores dosis de diuréticos y presencia de diabetes mellitus predisponen al desarrollo de ARI en pacientes con fallo cardiaco. Esto resalta la importancia de ajustar las dosis de diuréticos durante el tratamiento en estos pacientes.

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