Relationship of Loop Diuretic Dosing and Acute Changes in Renal Function during Hospitalization for Heart Failure

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Abstract

Background: Worsening renal function (WRF) during heart failure (HF) hospitalization is an accepted correlate of poor prognosis. Loop diuretics are increasingly being considered as a potential cause of worsened HF outcomes, perhaps via WRF. However, the magnitude of worsening in renal function attributable to loop diuretics has not been quantified.

Methods: This was a retrospective cohort study of patients who received care from a large health system and had a primary hospital discharge diagnosis of HF between Jan 1, 2000 and June 30, 2008. Patients with preexisting end-stage renal disease were excluded. Daily creatinine (Cr) measurements, furosemide dosing (only loop diuretic on hospital formulary), and radiocontrast dye studies were collected using administrative data. Day-to-day changes in Cr and MDRD estimated glomerular filtration (eGFR) were calculated. The first Cr or eGFR value during hospitalization or in the emergency department was considered baseline. Generalized estimating equations were used to test the association furosemide exposure over previous 2 days to the daily change in Cr and eGFR. Covariates included undergoing radiocontrast study, age, race, gender, and baseline Cr or eGFR.

Results: Among 6071 patients who met inclusion criteria there were a total of 20,645 observations. This cohort was 51% female, 68% African American, and baseline Cr was 1.36 mg/dl. Furosemide exposure was associated with an average daily increase in Cr of 0.021 mg/dL and decrease in eGFR of 0.72 ml/min/1.73m^2 (per 100 mg furosemide daily, both $p<0.001$). Over a typical length of stay of 5 days this would amount to a Cr increase of 0.11 mg/dL or decrease in eGFR of 3.6 ml/min/1.73m^2. Furosemide exposure accounted for only 0.4% and 0.1% of the variation in Cr and eGFR changes, respectively. Undergoing radiocontrast study, African American race, and higher age were associated with day-to-day creatinine increases (all $p<0.01$). Reanaysis after classifying furosemide exposure into low (<40mg/day), medium (40-100mg/day), and high (>100mg/day) and censoring patients-days after radiocontrast exposure did not significantly affect the magnitude of the worsening renal function.

Conclusions: While loop diuretic exposure is statistically associated with WRF among hospitalized HF patients, the associated magnitude of renal function change is very small, and loop diuretics explain little of the variability in renal function during hospitalization. More important explanatory factors likely exist but remain unidentified.

Introduction

Worsening renal function (WRF) during heart failure (HF) hospitalization is an accepted correlate of poor prognosis. It is associated with prolonged length of hospital stay, increased healthcare costs, increase in-hospital mortality, and higher rates of re-hospitalization and death post-discharge [1,2]. Loop diuretics are also increasingly being considered as a potential cause of worsened HF, perhaps via WRF. It is well established that loop diuretic dose is associated with poor outcomes in patients with HF [3-5]. In clinical practice, it is often noticed that creatinine (Cr) can rise with diuresis, though whether these associations amount to causation is subject of intense debate and continued research.

There are data to support the notion that loop diuretics have direct adverse affects on renal function and HF outcomes. Loop diuretics acutely can cause a decrease in glomerular filtration and reduce renal blood flow due to activation of the sympathetic renin-angiotensin-aldosterone systems [6,7]. Furthermore, chronic loop diuretic exposure has been noted to be accompanied by structural changes in the kidneys, such as hypertrophy of the epithelial cells in the distal convoluted tubules [8] as well as diuretic resistance [9]. On the other hand, it is also clear that the response to diuretics is reduced in patients with more severe HF and/or worse baseline renal function, [10,11] and therefore, higher doses of diuretics may simply be a marker of disease severity.

In the context of this uncertainty, an important piece of information still missing is the degree to which acute WRF is attributable to loop diuretic therapy. This is a key piece of information because it could shed additional light as to whether loop diuretics contribute to worsened outcomes and thus whether randomized studies to establish safety and efficacy or alternative approaches to volume control in HF

are truly required. Few studies have focused on whether and how much WRF during hospitalization is attributable to loop diuretic dosing, rather most address overall risk and correlates [12,13]. Interestingly, the recent DOSE trial evaluated the effect of high vs. low dose diuretics on change in creatinine and found no lasting deterioration due to high dose diuretic, though its power to detect important changes may be limited due to cohort size (n=308) [14]. We aimed to answer this uncertainty by conducting a retrospective analysis of a large cohort of patients hospitalized for HF, focusing on the short term (i.e. day to day) relationship of loop diuretic dosing with changes in renal function during heart failure hospitalization, and quantifying the strength and magnitude of this association.

Methods

Study population

The study was approved by the institutional review board (IRB) at Henry Ford Hospital. We identified a retrospective cohort of 6071 patients with a primary diagnosis of HF, who were discharged from a large, urban medical center between Jan 1, 2000 and June 30, 2008. Primary hospital discharge diagnoses have been shown to have very high specificity for clinical heart failure [15,16]. HF hospitalizations were identified with principal discharge diagnosis (International Classification of Disease, ninth revision [ICD-9] codes: 428.0, 428.1, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, and 404.93) as described elsewhere [17,18]. The index hospitalization was the first inpatient admission during the period of observation (i.e. subsequent admissions for an individual patient were not included). Patients with preexisting end stage renal disease (defined as history of receiving dialysis, and those with an estimated Glomerular Filtration Rate [eGFR] of <15 using the Modification of Diet in Renal Disease formula [19] were excluded. Data was collected from electronic administrative databases maintained by the health system. Laboratory studies performed within the health system, furosemide dosing (furosemide is the only loop diuretic available on hospital formulary), and radio-contrast dye studies were accessible through the database. WRF was defined as a ≥ 0.3 mg/dl increase in Cr on any subsequent hospital day as compared to the previous day [20].

Statistical approach

Day-to-day changes in Cr values and calculated and changes in the eGFR, were collected for the study population. The first Cr value obtained either in the emergency department (ED) or during hospitalization was considered the baseline value. This results in roughly one observation for each patient-day in the hospital, for a total of 20,645 observations in this data set. We calculated the total furosemide dose in milligrams (mg) over the preceding two days for each day of inpatient follow up. To combine oral and intravenous doses we first multiplied by the bioavailability proportion of 0.55 then summed. Other covariates including age, race, gender, and the presence of a radio-contrast study over the preceding two days, baseline Cr and eGFR were collected.

Generalized Estimating Equations (GEE) were used to assess for the association between furosemide exposure over the previous two days and the day-to-day change in Cr. Covariates of age, gender, race, and recent radio-contrast study were included in the models in order to account for possible confounding. An illustrative example of our approach for a single patient is shown in Figure 1. P-values less than 0.05 were considered statistically significant. All analyses were performed in SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics of the study population are included in Table 1. The average age of the subjects was 67.5 ± 15.5 years. Approximately half of the study participants were women. African American individuals compromised 63.5% of the cohort. On average patients received 60 mg/day of furosemide. Average baseline Cr and eGFR were 1.36 and 67.4, respectively, and 7.6 % of the patients were administered radio-contrast during admission.

Table 2 shows the results of the adjusted GEE models relating two-day furosemide exposure to the change in Cr and eGFR. The amount of furosemide exposure over the previous 2 days was a highly significant correlate of day-to-day changes in Cr and eGFR (both with p<0.001). Baseline renal function and age were also independently associated with day-to-day changes in Cr and eGFR (both p<0.01). Conversely, African American race and receiving radio-contrast were associated with a rise in Cr (both p<0.01) but were not significantly associated with changes in eGFR. Exploratory analyses examining interactions between age, race, gender and furosemide dosing did not find statistically significant interactions (all p>0.05) suggesting that the effect of furosemide does not differ between these subgroups.

Despite furosemide exposure being highly statistically significant in association with changes in renal function, the magnitude of this association was in fact quite modest (Table 3). On average, exposure to an additional 100mg of furosemide daily was associated with a daily increase in Cr of 0.021 mg/dl or a decrease in eGFR of 0.724 ml/min/1 73m². Thus, with a typical length of stay of 5 days, an additional 100 mg of furosemide daily would be expected to result in a modest increase in Cr of 0.11 mg/dl, or an average decrease in eGFR of 3.7 ml/min/1.73 m².
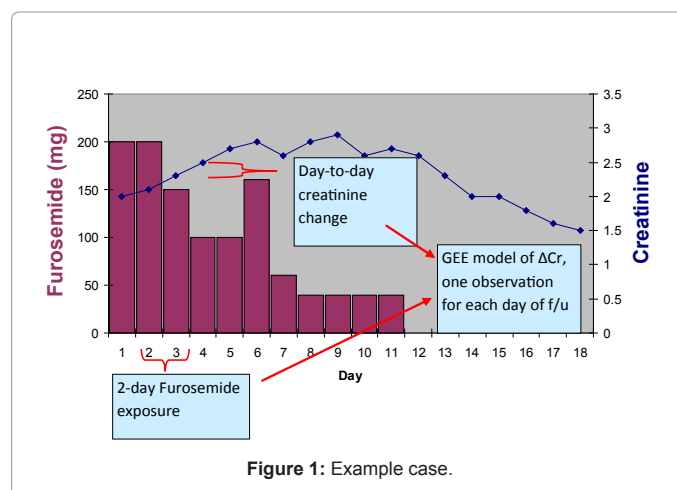

Figure 1: Example case.

Variable	Value	SD	Min	Max
Age (years)	67.5	15.5	18	109
Female (%)	50.7	NA	NA	NA
African American (%)	63.5	NA	NA	NA
Length of Stay (days)	5.4	7	1	168
Radio-contrast Study (%)	7.6	NA	NA	NA
Baseline Creatinine (mg/dl)	1.36	0.66	0.2	5.5
Baseline eGFR (ml/min/1.73 m²)	67.4	31.8	12.9	518.1
Average Furosemide Dose In Hospital (mg/day)	89.6	100.7	0	1120
Daily Creatinine Change (mg/dl)	0.024	0.34	-7.1	6.5
Daily eGFR Change (ml/min/1.73 m²)	-1.11	18.67	-922	917

Table 1: Characteristics for N=6071 Patients (20,645 observations).

Variable	eGFR models			Creatinine models		
	β	P-value	Model R^2	β	P-value	Model R^2
Furosemide exposure (100mg)	-0.724	0.001	0.001	0.021	0.001	0.003
Baseline renal function	-0.061	0.001	0.020	-0.020	0.001	0.003
Radio-contrast	-1.046	0.073	0.020	0.032	0.003	0.004
Age	-0.039	0.001		0.001	0.001	
African American	-0.175	0.511	0.021	0.014	0.003	0.005
Female	-0.514	0.050		-0.005	0.312	

Table 2: GEE Model Results.

	Day to Day Creatinine			Day to Day eGFR	
Variable	β	p-value	Variable	Est	p-value
Furosemide <40			Furosemide <40		
Furosemide 40-100	0.041	0.001	Furosemide 40-100	-1.443	0.001
Furosemide >100	0.058	0.001	Furosemide >100	-1.967	0.001
Age	0.001	0.001	Age	-0.037	0.001
Black	0.014	0.005	Black	-0.176	0.507
Female	-0.005	0.324	Female	-0.477	0.069
Contrast	0.031	0.004	Contrast	-0.992	0.088
First Creatinine	-0.017	0.001	First eGFR	-0.059	0.001
Furosemide (>100) vs Furosemide (40-100)	p- value = 0.013		Furosemide (>100) vs Furosemide (40-100)	p-value = 0.096	

Table 3: Effect on of Furosemide Stratified by Dose.

Notably, furosemide exposur accounted for only 0.5% of the overall day-to-day variability in eGFR, while the entire model explained only 2% of the variability in eGFR.

To better evaluate the robustness of our findings we performed several secondary analyses. While the effect of radiocontrast dye on the renal function was accounted for in the base model, we repeated our analysis with censoring for the patients-days after radiocontrast study in order to eliminate any possibility of residual confounding, much like the base model, the result was a statistically significant worsening in creatinine of only modest magnitude, with an average day to day change in creatinine of 0.02 mg/dl due to furosemide exposure (p=0.001). Finally, we also considered the possibility of a non-linear dose-effect. Models similar to those described above but with furosemide exposure classified as low (<40mg/day; 7218 observations, 31.1%), medium (40-100 mg/day; 8833 observations, 38.1%) or high (>100mg/day, 7130 observations, 30.8%) were constructed. There was a statistically significant worsening of renal function in both the medium and high dose groups in comparison to the <40mg/day group, with average rise in creatinine of 0.041 mg/dl and 0.058 mg/dl per day, respectively (both p< 0.001). If taken over a typical 5 day admission this would be expected to amount to 0.2 to 0.3 mg/dl rise in creatinine.

Discussion

Although the association between loop diuretics, in this case furosemide, and changes in renal function in hospitalized HF patients is highly statistically significant, the magnitude of this change is very small, amounting to roughly 0.2 mg/dL change over a typical HF hospitalization. Furosemide and the entire model accounted for roughly only 1% of the variation in the Cr and eGFR. This suggests that despite a statistically significant association, on average furosemide is unlikely to play a clinically important role in WRF in patients hospitalized for HF. Furthermore, these data underscore the inadequacy of our understanding of acutely worsening renal function in HF, since the multivariate model which included several statistically significant factors such as radiocontrast, age, race and loop diuretic failed to predict a large portion of the acute changes in renal function.

It's essential to view our data in the context of existing studies. Most important is the recent DOSE study [14], one of the very few randomized trials to examine diuretic therapy in hospitalized heart failure patients. One of the primary goals was to examine the effect of high dose versus low dose intravenous furosemide, where rise in Cr was a co-primary endpoint. The results showed no significant or lasting difference in serum Cr between the groups. Our data are consistent with these as we found very little change in Cr attributable to diuretic dose. Our approach was focused on day-to-day changes in renal function during heart failure exacerbation, because this is a period of vulnerability for the kidney during which WRF is common. Therefore, it needs to be kept in mind that our data do not address whether more chronic loop diuretic exposure (e.g., over months to years) might indeed have clinically relevant adverse impacts on renal function.

Limitations of this study must be taken into consideration when interpreting the results. The usual limitations of retrospective studies apply, such as the inability to determine causality and the possibility that we did not account for important confounders. The accuracy of the claims in defining HF could be questioned; however, we and others have shown that a primary discharge diagnosis of HF is 95%-100% specific in excluding alternative diagnoses [14,18]. Other limitations include the inability to account for systolic vs. diastolic dysfunction due to absent cardiac function data. Nevertheless, no previous study has described differential renal effects based on cardiac ejection fraction. We chose a two-day window for analysis thinking that this would be the best window to see the immediate relationship between furosemide administration and renal function; however, other time frames may be more appropriate. The consistency of our findings with those of others suggests that our time frame may have been sufficient. We did not have access to pre-hospitalization medication use so the impact of home dose on these findings is unknown. Finally, our administrative data did not allow us to distinguish between intravenous furosemide as continuous infusion versus bolus dosing. While in theory this could impact our analysis towards the null, the DOSE study examined this issue in a randomized fashion and found no difference in renal function between these modes of administration [14].

In conclusion, our data suggest that furosemide dosing during a hospitalization for heart failure does not have a large clinical impact on renal function, despite having a statistically significant association. This suggests that additional research towards examining diuretic renal effects or replacing loop diuretics as the primary method of controlling fluid overload may not be as fruitful as is hoped. Our data do not address renal effects of chronic loop diuretic exposure which should remain a source of debate. Equally important is the fact that several statistically significant correlates of renal function change (furosemide dose, age, race, and radiocontrast administration) even when modeled together accounted for only a tiny portion of the daily variability in renal function. This indicates that the key determinants of acute renal function changes in HF patients are yet to be identified. Defining these factors should be a high priority for future study given the poor prognosis that WRF portends for patients with heart failure.

Acknowledgements

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