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Preventable delays to intravenous furosemide administration in the emergency department prolong hospitalization for patients with acute heart failure

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ABSTRACT

Background: We sought to examine whether factors impacting the time to emergency department (ED) administration of intravenous (IV) furosemide were associated with the duration of hospital admission for patients with acute heart failure (AHF).

Methods and results: We conducted a single-center, retrospective analysis of patients presenting to the ED and admitted between January 1, 2007 and December 31, 2014 who received a dose of IV furosemide. A Cox proportional hazards model was used to examine the likelihood that a patient would be discharged home alive, adjusting for patient demographics, AHF severity (low, moderate, high), laboratory result timing, and known AHF confounders. We identified 695 patients who met study criteria with 430 (61.9%) in the low-severity group. In the overall model, every 60-minute delay in IV furosemide administration was associated with an 8% lower chance of successful discharge home relative to someone who received early furosemide (aHR 0.93, 95% CI 0.87, 0.98, P = 0.012). Subgroup analysis suggests this association was most impactful in low-acuity patients. Our adjusted analysis suggests delaying furosemide administration until after serum creatinine results resulted in a 41% lower chance of successful discharge home relative to someone who had furosemide administered prior to creatinine results (aHR 1.41, 95%CI 1.07, 1,84).

Conclusions: AHF patients, particularly those with lower severity, may benefit from rapid administration of IV furosemide in the ED. This suggests that a key determinant of hospital visit duration in this low-risk cohort is decongestion, which occurs sooner when IV therapy is begun early in the ED stay regardless of serum creatinine.

1. Introduction

Heart failure is a chronic, costly, debilitating, and deadly disease with an annual mortality rate of 10% that increases in prevalence as individuals age [1]. The emergency department (ED) plays an important role in acute heart failure (AHF) management and resource use. In the U.S., there are an estimated one million ED visits annually for AHF [2, 3], and over 80% of heart failure patients continue to be admitted by ED providers [2]. Of the $39 billion in annual U.S. expenditures for heart failure care [1], the single largest proportion is due to hospitalization [4, 5], costing the U.S. $11 billion annually [6] and affecting 5–6 million people [3, 7]. While the ED plays a vital role in the decision to admit AHF patients, little research has explored the role of ED care on downstream clinical and operational outcomes for patients with AHF.

Prior research suggests a relationship between early initiation of intravenous (IV) AHF therapy in the ED with beneficial clinical and operational outcomes [8–10]. ED administration of IV vasoactive agents reduced in-hospital mortality within the first 48 h of admission [8]. ED treatment delays with IV diuretics were modestly associated with increased in-hospital mortality [9]. Similarly, delays to first IV AHF treatment (loop diuretics, inotropes, or vasodilators) in ED patients over 65 years of age hospitalized with AHF were associated with higher in-hospital mortality and longer inpatient length of stay, but were not associated with 30-day outcomes [10]. Finally, among 1291 patients treated with IV furosemide after presenting to the ED, those who were treated within 60 min of arrival to the ED had significantly reduced odds (0.39, 95%CI 0.2, 0.76) of in-hospital mortality [11].

However, these prior studies have limitations that make their applicability regarding timing of furosemide administration to ED patients

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difficult to interpret, such as: 1) selecting only patients eligible for Medicare [10], and those in practice settings that have disproportionately longer lengths of stay [11]; 2) analyzing patients who receive a combination of IV furosemide and IV vasoactives; and 3) evaluating in-hospital mortality as the primary endpoint.

Considering the aforementioned limitations, our objective was to evaluate the relationship between the timing of ED administration of IV furosemide and likelihood of successful discharge home from the hospital in a broad setting of AHF presenting to the ED for emergency care.

2. Materials and methods

We conducted a retrospective analysis of ED patients presenting with AHF to Vanderbilt University Medical Center (VUMC), an academic, tertiary care, level 1 trauma center in Nashville, TN, USA. There is a heart failure program at VUMC providing surgical and non-surgical care to patients with heart failure. This study was approved by the VUMC Institutional Review Board.

Data were extracted from the VUMC Enterprise Data Warehouse (EDW). The variables extracted included patient demographics, clinical variables regarding AHF treatment, and operational data about timing and duration of care in the ED and inpatient settings. Considering that all patient mortality data may not be reported in the VUMC EDW, we also searched the Social Security Death Index for patient mortality. Inclusion and exclusion criteria followed existing clinical research standards for studies of AHF patients in the ED [12]. We wanted to include a patient population not only felt to have AHF in the ED, but also had a diagnosis of AHF once they were admitted. We felt this was important in an analysis investigating timing of medication administration, because if either the ED or inpatient teams did not diagnose AHF, both the timing of treatment and the patient's hospital length of stay could be affected.

Patients were included in this study if presented to the VUMC ED between January 1, 2007 and December 31, 2014. Patients had to have a primary, secondary, or tertiary ED diagnosis combined with a primary, secondary, or tertiary inpatient diagnosis of heart failure defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) classification codes (428.x, 428.xx, 402.x1, 404.x1, and 404.x3). Patients had to have at least one dose of IV furosemide administered while in the ED, although other diuretics could also be administered (e.g., bumetanide) during their ED stay. Patients were required to have a b-type natriuretic peptide (BNP) level drawn while in the ED, enhancing the likelihood that AHF was in the differential diagnosis while enabling a secondary analysis of the association between treatment administration and timing of BNP results. However, we did not require a specific level as this may be confounded by renal function [13] or body mass index [14].

If patients did not initially present to the ED or were transferred from another facility, they were excluded from the analysis. Initial care at another facility may introduce confounders into our results due to variability in practice patterns at other institutions. Moreover, prolonged transfer times may also diminish treatment effects. Of note, we did not exclude patients if they presented with a subsequent AHF exacerbation. We reasoned that the prior episode had resolved and re-presentation was distinct.

2.1. Analysis

Our objective was to examine the relationship of timing of IV furosemide administration timing with the likelihood of successful discharge home. Since length of stay in healthcare is subject to the competing risk of death (i.e., a shorter length of stay is not always better), the analysis had to simultaneously consider patient mortality. While some patients may not die, aggressive efforts to treat the patient may cease if the patient has advanced directives indicating that no additional treatments should take place, or that the patient and/or family has decided to go to hospice for end-of-life care. To account for the competing risk of expected or actual death, we modeled the cause-specific hazard of discharge home alive using Cox proportional hazard model [15].

Applied to our study on IV furosemide administration timing, the primary outcome was the timing of successful discharge home alive for an admitted AHF patient. As we used a cox proportional hazard model, we defined the time period of hospitalization as the duration from the hospital admission order until the hospital discharge was ordered by the treating physician. We defined the censoring event included in our survival analysis as any of the following: 1) death; 2) hospice care; and 3) transfer to another institution. We included transfer because complete records may not be available after the patient leaves the hospital. In addition, since we did not use multiple groups to compare their relative hazards, we used the timing of IV furosemide administration for all included patients.

The following potential confounders were included as covariates: patient age, sex, and insurance status (Medicare, Medicaid, Private, Other). To account for severity of illness, we adapted a measure of AHF severity from Fonarow et al. [16], which used hospitalization data from the Acute Decompensated Heart Failure National Registry (ADHERE), as the count of the following: lowest systolic blood pressure < 115 mm Hg, blood urea nitrogen level ≥ 43 mg/dL, plasma creatinine ≥2.75 mg/dL, and elevated troponin. Although troponin was not one of the identified variables, we included it as prior work has identified sensitive troponin as a prognostic indicator of AHF prognosis [17]. As no formally accepted decision aid exists to risk stratify AHF patients, we used the count of these predictors as an indicator of low (zero factors), intermediate (one factor), and high (two or more factors) severity of AHF. We also included emergency severity index (ESI) triage level as the initial assessment by the ED staff of the overall acuity of the patient at triage, intensive care unit (ICU) admission from the ED, admission to a cardiology service from the ED, arrival by emergency medical services, cumulative IV administered dose of furosemide in the ED, order-to-administration time interval of furosemide before/after the BNP result, and, finally, order-to-administration time interval of furosemide before/after creatinine result. For the laboratory results, we reasoned that some emergency clinicians may wait to administer furosemide until either of these tests returned results so we included indicator variables of both BNP and creatinine testing. Subgroup analyses for AHF severity were planned as severity was reasoned to influence the timing of furosemide administration. The proportional hazards assumption was checked for each variable based on scaled Schoenfeld residuals [18].

3. Results

There were 695 patients between January 1, 2007 and December 31, 2014 who directly presented to the ED at VUMC, had both an ED and inpatient diagnosis of AHF, and had a BNP drawn in the ED. The identification of the study population can be seen in Fig. 1 and patient demographics can be seen in Table 1. Approximately one-third of subjects in the initial database of 1043 were excluded for discordance between the ED and inpatient diagnoses of heart failure, approximately another third for not receiving an IV dose of furosemide, and the remainder of the original dataset (55, 5.3%) were excluded for either missing data such as adjusting variables or outcomes of interest. Of the final subjects included in the study, nearly two-thirds corresponded with the lowest severity, one quarter were moderate-severity (one severity marker), and the remainder were high-severity (two or more severity indicators). The majority of included patients were white males, with a median age of 66 years. Length of stay in the ED for admitted AHF patients similarly decreased in duration as AHF severity increased. The median inpatient length of stay from ED disposition through hospital discharge was between 3 and 4 days. Finally, 30-day mortality increased as AHF severity increased.

Examining the timing of care provided in the ED (Table 1), 82% of patients received only one IV medication (i.e., furosemide) during their ED stay with the remainder of patients receiving two or more IV medications. The arrival-to-bed placement interval for this population was between 10 and 12 min. On average, most patients received an initial IV treatment with furosemide under 3 h and this duration decreased as AHF severity increased. Patients with AHF were also more likely to receive a higher cumulative dose of IV furosemide as their severity increased. Nearly two-thirds of patients received IV furosemide after BNP results and almost 80% of AHF patients in the ED received IV furosemide after creatinine results were available.

In order to better understand the timing of IV furosemide administration, we calculated descriptive statistics by the variable of interest (Supplemental Table 1). Patients with AHF had significantly shorter arrival-to-furosemide durations if they arrived to the ED by EMS, were eventually admitted to a cardiology team or to the ICU, received two or more IV medications while in the ED, or received IV furosemide before BNP or creatinine laboratory testing results were available. However, administration times were similar by severity level (Fig. 2).

In our Cox regression models, the proportional hazards assumption was met. In the overall model (Table 2, first column), the arrival-to-furosemide duration variable was significantly related to hospital length of stay ($P = 0.012$) with an adjusted hazard ratio (aHR) of 0.93 (95% CI 0.92, 0.93). Every 60-minute delay of IV furosemide administration was associated with an 8% lower chance of being discharged to home during their hospital stay. Administration of IV furosemide prior to creatinine laboratory results was the only variable that remained significant in: 1) the overall, 2) interaction, and 3) low-severity models.

To examine whether the relationship between timing of furosemide administration and likelihood of hospital discharge may be dependent upon AHF severity independently, we developed another model with an interaction term for severity with the low-severity group as the referent. In this model, only the arrival-to-furosemide duration in the

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