ABSTRACT

Background: Diuresis is the mainstay of treatment during hospitalization for patients admitted with congestive heart failure (CHF). Hospital length of stay (LOS) is considered an important patient outcome for CHF patients; previous studies comparing higher rates of diuresis (aggressive) versus relatively lower rates (nonaggressive) on patient outcomes have shown contradicting results. In fact, no specific guidelines to direct diuretic therapy exist. This investigation was designed to study the effect of early aggressive diuresis on hospital LOS.

Methods: Data from 194 CHF patients (admitted to the hospital for 1 year) were collected and analyzed in a retrospective cohort study design. Patients were divided into two cohorts based on urine output achieved in the first 24 h of admission; the aggressive diuresis cohort (urine output ≥2400 mL) comprised of 29 subjects while the nonaggressive diuresis cohort (urine output ≤2400 mL) had 165 subjects. The primary endpoint was LOS.

Results: Median LOS for the aggressive diuresis cohort was 4 days (95% confidence interval [CI]: 2.95–5.06) as compared to 5 days (95% CI 4.40–5.60) for the nonaggressive diuresis cohort; log-rank test showed no significant differences between the hospitalized proportions between the two cohorts over time (P = 0.67).

Conclusion: Hospital LOS for CHF patients treated with early aggressive diuresis was not significantly different compared to patients treated with nonaggressive diuresis.

Key words: Congestive heart failure, diuresis, hospital length of stay

INTRODUCTION

Congestive heart failure (CHF) can be thought of as a pandemic that exerts significant health and economic burden on society. It affects roughly 6.5 million people in the United States and 26 million around the world. Hospitals are particularly affected as CHF patients are frequently admitted requiring a higher level of care; in fact the re-admission rate is estimated to be 25% within 30 days of a recent hospital discharge, adding significant costs to the health care system. It is estimated that the costs of CHF admissions contribute to around 1.5% of the annual health care budget for most Western countries. Hospitals are constantly trying to improve patient outcomes and reduce costs. In

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the United States, Medicare-based reimbursement for hospitals for managing CHF admissions is tied to various quality measures such as hospital length of stay (LOS) and re-admission rates. Hospitals are penalized if they fail to meet standards. The hope is that optimal CHF treatment practices can be discovered so that important patient outcomes such as hospital LOS (US national average hospital LOS is estimated to be between 6–8 days for CHF patients) can be improved and subsequently financial costs can be lowered.

The mainstay of treatment for patients admitted with CHF is diuretics. Clinical improvement results when symptoms of congestion are relieved with diuresis. Symptomatic relief and patient outcomes are directly related to the absolute urine output rather than the dose of diuretics administered. Loop diuretics are considered the primary class of diuretics for CHF.

In clinical practice, factors such as dose, frequency, and route of administration of diuretics vary considerably and optimal diuresis guidelines to direct best practices do not exist. Many clinical studies have been conducted in the past comparing the effect of aggressive versus nonaggressive diuresis strategies on patient outcomes, yielding mixed results.

Previously, the DOSE trial observed the effect of varying doses of diuretics on hospital LOS. Results from the DOSE trial did not show a difference on the overall LOS even when higher doses of diuretics were administered. Other investigations such as Howard and Dunn and Li and Hong showed that aggressive diuresis did indeed lead to a shorter LOS. In the backdrop of such inconsistencies we decided to compare the effect of early aggressive diuresis on hospital LOS against nonaggressive diuresis.

METHODS

Study design and population
We used a retrospective cohort study model. Patients admitted to the medical ward or cardiac care unit with CHF between the years 2014 and 2015 were identified retrospectively using the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) diagnosis code.

Patients aged between 18 and 80 years who fulfilled the CHF diagnosis criteria with; elevated filling pressures, presence of at least one relevant symptom, and the presence of at least one relevant physical examination finding were included. We did not use the ejection fraction of the heart as part of our inclusion criteria. We included both; initially diagnosed and chronic patients with exacerbation of CHF.

We excluded patients if they had; history of ESRD on dialysis, history of chronic obstructive pulmonary disease, asthma exacerbation on presentation, creatinine >2.0 mg/dl on presentation, cardiogenic shock (defined as systolic blood pressure [BP] <90 mm Hg and requiring hemodynamics support) or acute coronary syndrome on presentation.

Data collection and organization
Each patient was followed for 30 days from the day of admission and relevant data were recorded. Patients were censored if they died during the hospitalization or if they were still admitted till the end of the study period (December 31, 2015).

We collected data for; demographic details, systolic BP on presentation, serum creatinine level on presentation, left ventricle ejection fraction, type of CHF (systolic or diastolic), method of delivery of furosemide in the first 24 h (intravenous bolus or continuous infusion), amount of urine output in the first 24 h of admission (in milliliters), and adverse events (arrhythmias, worsening renal function, hypotension).

We then categorized the patients into two categories; the aggressive diuresis group (urine output ≥2400 mL in the first 24 h) and the nonaggressive diuresis group (urine output ≤2400 mL in the first 24 h).

Endpoint
The primary endpoint was hospital LOS.

Statistical analysis
Study size and power estimates were based on the median number of days of hospital stay using the log-rank test method. Based on 450 admissions in the hospital each year, we expected 90% power. Type 1 error level was chosen as 0.05 for a two-sided hypothesis.

Normally distributed data were presented as mean and standard deviation, while nonnormal data were presented as median and interquartile range (IQR). Categorical data were presented as frequencies and percentages. We cross-tabulated categorical variables with Chi-square test to determine whether the observed distribution fitted the expected distribution when cell size was sufficient. When the cell size was not enough, Fisher’s exact test was used. For continuous covariates, independent sample t-test was used to compare the mean between the aggressive and the nonaggressive diuresis groups for normally distributed data, whereas Mann – Whitney U test was used for nonnormal data.

In multiple linear regression model, we defined the predictors of 24-h urine output by regressing the 24-h urine output as a continuous outcome variable on the 24-h furosemide dose.

Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval for hospital discharges in the aggressive versus nonaggressive diuresis groups.

Nonparametric Kaplan Meir method was used to compare the proportion of patients discharged from the
hospital between the aggressive and the nonaggressive diuresis groups. Survival curves were compared using log rank and Breslow tests.

Statistical analysis was performed with SPSS version 24.0 and SAS version 9.4 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp, and SAS version 9.4.). Significance was defined as the two-tailed value of $P < 0.05$.

RESULTS

A total of 483 patients met the screening criteria. Of the 483 patients, we excluded 289 cases, leaving 194 patients. Of the 194, 29 fell into the aggressive diuresis group, while 165 came under the nonaggressive diuresis group [Figure 1]. Follow-up was complete in all cases. Six patients died in the nonaggressive diuresis group and were censored from the final analysis.

In the entire cohort (including both groups), the range of urine output in the first 24 h ranged from 110 to 5800 mL with a mean of 1372 ± 1009 mL. The total furosemide doses administered in the first 24 h ranged from 40 to 240 mg with a median dose of 80 mg (IQR 40–80). The total range of LOS was 1–28 days with a median of 5 days (IQR 3–8).

Distributions of age, sex, race, and types of CHF (systolic or diastolic) were similar between the two groups. The mean of the systolic BP on presentation was higher in the aggressive diuresis group as compared to the nonaggressive diuresis group (144±−23 vs. 135±−23; $P = 0.046$). The total dose of furosemide administered in the first 24 h was higher in the aggressive diuresis group versus the nonaggressive group ($P = 0.049$). The mean of the urine output in the first 24 h was higher in the aggressive diuresis group as compared to the nonaggressive group (3209 ± 903 vs. 1049 ± 598; $P = 0.001$).

The proportion of patients who developed kidney dysfunction was higher in the aggressive diuresis group as compared to the nonaggressive diuresis group, but it was not statistically significant (12.15% vs. 6.9%; $P = 0.2$). The proportion of patients with an episode of hypotension was higher in the nonaggressive diuresis group as compared to the aggressive diuresis group, but it was not statistically significant (6.9% vs. 13.9%; $P = 0.38$). Six deaths were recorded in the nonaggressive diuresis group was compared to none in the aggressive diuresis group [Table 1].

The final multivariable linear regression model after backward elimination showed a statistically significant main effect ($P < 0.001$) of the dose of furosemide in increasing the initial 24 h urine output along with its interaction with serum creatinine at the time of admission [Supplementary Table 1]. A higher dose of furosemide was required to produce the same amount of urine if the serum creatinine on presentation was >1.6 mg/dL [Figure 2].

In univariate analysis, Cox proportional hazards regression showed that the effect of aggressive diuresis on the unadjusted hazard rate of hospital discharge was not statistically significant (HR = 1.08; $P = 0.70$) [Supplementary Table 2].

In multivariate analysis, Cox proportional hazards regression showed that the effects of; creatinine at the time of admission when >1.6 mg/dL ($P = 0.75$), left ventricular ejection fraction ($P = 0.14$), total 24 h dose of furosemide administered ($P = 0.98$) and interaction between furosemide and creatinine ($P = 0.79$), on the risk of hospital discharge were not statistically significant [Supplementary Table 3].

The adjusted hazard rate of discharge from the hospital was 12% higher in the aggressive diuresis
Table 1: Characteristics of patients

| Characteristics                          | Cohort                   | Nonaggressivediuresis* | Aggressivediuresis* | P     |
|------------------------------------------|--------------------------|------------------------|---------------------|-------|
| Age (years), mean (SD)                   | 72 (11)                  | 72 (10)                | 69 (12)             | 0.09  |
| Race                                     |                          |                        |                     |       |
| White                                    | 182 (93.8)               | 153 (92.7)             | 29 (100)            | 0.22  |
| Non-White                                | 12 (6.2)                 | 12 (7.3)               | 0                   |       |
| Sex                                      |                          |                        |                     |       |
| Male                                     | 96 (49.5)                | 80 (48.5)              | 16 (55.2)           | 0.51  |
| Female                                   | 98 (50.5)                | 85 (51.5)              | 13 (44.8)           |       |
| Type of CHF                              |                          |                        |                     |       |
| Systolic                                 | 112 (57.7)               | 96 (58.2)              | 16 (55.2)           | 0.76  |
| Diastolic                                | 82 (42.3)                | 69 (41.8)              | 13 (44.8)           |       |
| LVEF (%), mean (SD)                      | 40 (16)                  | 40 (16)                | 41 (15)             | 0.78  |
| Systolic blood pressure on admission (mmHg), mean (SD) | 137 (23) | 135 (23) | 144 (23) | 0.046* |
| Creatinine at time of admission (mg/dL), mean (SD) | 1.33 (0.57) | 1.33 (0.56) | 1.31 (0.63) | 0.86  |
| Dose of furosemide used (mg), median (IQR) | 80 (40-80) | 70 (40-80) | 80 (55-120) | 0.049* |
| 24 h urine output (mL), mean (SD)        | 1372 (1009)              | 1049 (598)             | 3209 (903)          | <0.001* |
| Worsening of kidney function             |                          |                        |                     |       |
| Yes                                      | 22 (11.3)                | 20 (12.15)             | 2 (6.9)             | 0.54  |
| No                                       | 172 (88.7)               | 145 (87.9)             | 27 (93.1)           |       |
| Hypotension                              |                          |                        |                     |       |
| Yes                                      | 25 (12.9)                | 23 (13.9)              | 2 (6.9)             | 0.38  |
| No                                       | 169 (87.1)               | 142 (86.1)             | 27 (93.1)           |       |
| Death                                    |                          |                        |                     |       |
| Yes                                      | 6 (3.1)                  | 6 (3.6)                | 0 (0)               | 0.59  |
| No                                       | 188 (96.9)               | 159 (96.4)             | 29 (100)            |       |
| Arrhythmia                               |                          |                        |                     |       |
| Yes                                      | 9 (4.6)                  | 8 (4.8)                | 1 (3.4)             | 1     |
| No                                       | 185 (95.4)               | 157 (95.2)             | 28 (96.6)           |       |

*P (statistical significance: P < 0.05). CHF: Congestive heart failure, LVEF: Left ventricular ejection fraction, SD: Standard deviation

Table 2: Survival characteristics and length of hospital stay of the study sample

| Group                | Total number of patients | Total number of patients discharged | Total number censored | Median hospital stay (days), 95% (CI) |
|----------------------|--------------------------|------------------------------------|-----------------------|--------------------------------------|
| Aggressive diuresis  | 29                       | 29                                 | 0                     | 4 (2.95-5.06)                        |
| Nonaggressive diuresis | 165                     | 159                                | 6                     | 5 (4.40-5.60)                        |

CI: Confidence interval
group as compared to the nonaggressive diuresis group but was not statistically significant (adjusted HR = 1.12; \( P = 0.6 \)) Kaplan Meier estimate of the median accumulated proportion of patients still in the hospital in the aggressive diuresis group was 4 days as compared to 5 days in the nonaggressive diuresis group [Table 2]. Log-rank test (\( P = 0.67 \)) and Breslow test (0.77) showed no significant differences between the accumulated hospitalized proportion over time [Figure 3 and Supplementary Table 4].

**DISCUSSION**

Despite the discovery of some novel therapeutics, diuretics are still considered as the backbone of therapy in the treatment plan for a CHF patient admitted to the hospital.\(^{[22]}\) Furosemide is a loop diuretic and is the most widely utilized diuretic in clinical practice. As of yet no official guidelines exist for administering diuretics; doses, frequency, and route of administering diuretics vary greatly in clinical practice.

It is well-known that dose responses of diuretics can be unpredictable. Factors such as decreased bioavailability,\(^{[23]}\) diuretic resistance,\(^{[24]}\) and kidney dysfunction can cause inconsistent diuretic dose responses. The variations in the diuretic responses on urine output are important to consider because some previous studies (e.g., the DOSE trial) investigated the effect of the dose of diuretics on CHF outcomes without directly measuring the actual urine output. The assumption in such studies that diuretic doses always correlate with high urine outputs could have been potentially problematic because we understand that diuretic responses can be variable. In the backdrop of these concerns, we investigated the effect of the dose of furosemide on the first 24-h urine output in our study. We also analyzed the effect of renal function on the relationship of diuretic dose and urine output. The results of our study showed that higher doses of furosemide do result in higher urine outputs.

Furthermore, the renal function on presentation was an important factor in determining the response of diuretics; we found that the higher the creatinine, the higher the amount of diuretic dose needed to produce a given amount of urine output.

Another important factor that could potentially affect the efficacy of diuretics is concomitant use of other drugs such as nesiritide and dopamine (which are often given alongside furosemide in CHF); this was studied in the ROSE trial and the results showed no differences in urine outputs whether furosemide was used alone or when used along with dopamine or nesiritide.\(^{[25]}\) Although the ROSE trial did not show any effect of other drugs on furosemide efficacy, a true effect might well exist in reality; we did not study the effect of concomitant use of dopamine or nesiritide on diuretic responses in our investigation. Future studies could take this factor into account in their analysis.

Overall the findings of our study indicate that although diuretic responses are inherently heterogeneous (due to multiple factors), the dose of diuretics correlates fairly well with urine outputs achieved and that renal function is an important measurable factor that can modify this relationship.
Intuitively, it makes sense that higher diuretic doses result in higher urine outputs and subsequently improved patient outcomes and a shorter hospital LOS. The results from previous studies however had shown mixed results and it was clear that the association of aggressive diuresis with improved outcomes needed further investigation.

The DOSE trial studied the effect of the dose of furosemide on LOS (as a secondary outcome); the results showed no difference in LOS with varying doses.[8] The studies conducted by Howard and Dunn and Li and Hong used actual urine output to compare the effect of aggressive diuresis on LOS against nonaggressive diuresis; the results in these studies showed a shorter LOS in the aggressive diuresis group.[13,21]

It is of note that each study mentioned above was unique and tried to gauge patient outcomes with its own methodology. Some studies used diuretic doses while others used direct urine output as a measure of diuresis. Not only were these studies inherently different but they also yielded contradicting results. Hence, we cannot draw any conclusion on best diuresis practices from the results of the studies mentioned above or from numerous other studies conducted previously.

Our investigation is uniquely placed in this complex milieu. We not only used direct urine output but also employed a specific strategy of early (initial 24 h of admission) aggressive diuresis to study its effects on hospital LOS. The results and analysis of our study showed that the hospital LOS was not affected when patients were put on aggressive diuresis in the first 24 h as compared to a nonaggressive strategy. These results are in line with the DOSE trial which also did not show a shorter LOS with aggressive diuresis.

The results of our study, although not surprising, do bring up the question of why did aggressive diuresis not result in a shorter LOS. Although there could many reasons, one possible explanation to the results is that the aggressive diuresis cohort in our study could have experienced a higher rate of adverse effects. There are some well-known complications of aggressive diuresis such as hypotension, electrolyte imbalance, or worsening renal function documented in the literature. We hypothesize that the high rates of adverse effects in the aggressive diuresis cohort could have affected our results on two counts: first, they could have directly affected the LOS in the aggressive cohort; second, the high rates of side effects could have prompted the clinicians to adopt lower doses of diuretics after the initial 24 h, subsequently reducing the urine output even in the aggressive group after the initial 24 h, making the comparison of LOS with the nonaggressive group difficult. This fact that goes with the theory is that our study was not powered to detect statistical differences in adverse events between the two groups.

The results of our study should be interpreted in light of some limitations. First, the patients in this study represent a subset of the general CHF population (patients were selected from a single-center), this might have introduced a selection bias. Second, this study was not powered to detect statistical differences in adverse events between the groups that might have affected LOS in both groups. Third, our study focused only on the initial 24 urine output and did not take into account the urine output differences between the two groups for the entire LOS.

CONCLUSION

Early aggressive diuresis did not shorten the hospital LOS for patients admitted with CHF in our study. If future investigations can take into account the urine outputs for the entire hospital stay (instead of only the initial 24 h) and be powered to detect statistical differences in adverse events in the comparison groups, the effect of early aggressive diuresis on CHF patient outcomes can be better studied and possibly help unearth optimal diuresis practices.

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Conflicts of interest
There are no conflicts of interest.

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Supplementary Table 1: Multiple linear regression model with 24 h urine output regressed on dose of furosemide, creatinine at the time of admission

| Characteristics | Coefficient | SE     | 95% CI         | t    | P   |
|-----------------|-------------|--------|----------------|------|-----|
| Intercept       | 556.88      | 190.91 | 180.31-933.45  | 2.91 | 0.004 |
| Furosemide      | 12.14       | 2.43   | 7.35-16.94     | 5.00 | <0.001* |
| Cr >1.6         | 395.26      | 322.42 | −240.73-1031.25 | 1.23 | 0.22 |
| Cr >1.6 × furosemide | −8.98 | 3.47 | −15.83-−2.14 | −2.59 | 0.02* |

*Significant. Furosemide, Total 24 h dose of furosemide used in 24 h; Cr >1.6, indicates >1.6 mg/dL serum creatinine at time of admission equivalent to stage 3 or less kidney disease; Cr >1.6 × furosemide, indicates interaction between furosemide and creatinine >1.6 mg/dL. Cr: Creatinine, SE: Standard error, CI: Confidence interval

Supplementary Table 2: Univariate cox proportional hazards regression model showing effect of aggressive diuresis on risk of discharge from hospital

| Characteristics | Coefficient | SE     | Wald $\chi^2$ | P   | HR | 95% CI |
|-----------------|-------------|--------|---------------|-----|----|--------|
| Aggressive diuresis | 0.079 | 0.20   | 0.15          | 0.70 | 1.08 | 0.73-1.61 |

HR: Hazard ratio, SE: Standard error, CI: Confidence interval

Supplementary Table 3: Cox proportional hazards regression model showing the effect of four variables on risk of discharge from hospital

| Characteristics | Coefficient | SE     | Wald $\chi^2$ | P   | HR | 95% CI |
|-----------------|-------------|--------|---------------|-----|----|--------|
| Aggressive diuresis | 0.11  | 0.21   | 0.27          | 0.60 | 1.12 | 0.74-1.68 |
| LVEF            | 0.007      | 0.005  | 2.19          | 0.14 | 1.01 | 1.00-1.017 |
| Furosemide      | <0.001     | 0.003  | 0.001         | 0.98 | 1.000 | 0.995-1.005 |
| Cr >1.6         | −0.10      | 0.33   | 0.10          | 0.75 | 0.90 | 0.47-1.72 |
| Cr >1.6 × furosemide | 0.001 | 0.004  | 0.07          | 0.79 | 1.001 | 0.99-1.01 |

Aggressive diuresis, indicates ≥2400 mL/24 h urine. Furosemide, Total 24 h dose of furosemide used in 24 h; Cr >1.6, indicates >1.6 mg/dL serum creatinine at time of admission equivalent to stage 3 or less kidney disease; Cr >1.6 × furosemide, indicates interaction between furosemide and creatinine >1.6 mg/dL. LVEF: Left ventricular ejection fraction, HR: Hazard ratio, SE: Standard error, CI: Confidence interval, Cr: Creatinine

Supplementary Table 4: Summary of Kaplan-Meir estimate for cohort-total study sample of 194

| Time | Accumulated proportion of patients in the hospital (%) | 95% CI (%) | Total number of patients discharged | Total number of patients censored | Number at risk |
|------|------------------------------------------------------|------------|------------------------------------|----------------------------------|---------------|
| 2    | 0.80                                                 | 0.74-0.86 | 38                                 | 0                                | 156           |
| 4    | 0.53                                                 | 0.45-0.61 | 91                                 | 2                                | 101           |
| 6    | 0.32                                                 | 0.26-0.38 | 131                                | 0                                | 61            |
| 8    | 0.20                                                 | 0.15-0.26 | 153                                | 1                                | 38            |
| 10   | 0.15                                                 | 0.09-0.21 | 163                                | 1                                | 27            |