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Association between loop diuretic dose administered in first 24 hours of heart failure admissions and length of hospital stay

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ABSTRACT

Background: Heart failure remains one of the highest disease burdens in the USA and worldwide. Heart failure guidelines recommend starting with a higher or equal to home dose of loop diuretics in acute decompensated heart failure admissions. To date, no study has been published assessing the effect of first 24 h loop diuretic dose on length of hospital stay.
Objective: We hypothesize that the higher the first 24 h loop diuretic dose to home dose ratio, the shorter the length of hospital stay will be.
Design/Methods: Retrospective chart review was conducted in a community teaching hospital and included patients discharged between February, 2015 and April, 2016, with a primary diagnosis of acute decompensated heart failure. The primary outcome was the length of hospital stay. The study population was divided into three groups based on the hospital to home dose ratio.
Results: Among the 609 patients included in the data analysis, there was no statistically significant difference in length of hospital stay among the study groups. Inpatient mortality and incidence of acute kidney injury were highest in the group that received a first-24-hours hospital dose that was less than their home dose. Percentage of weight loss and 30-day readmission were not statistically significantly different among the groups.
Conclusion: There was no association between the dose ratio and length of hospital stay in each group. Additional randomized controlled trials need to be conducted to provide more evidence and guidance for dosing loop diuretics in acute decompensated heart failure admissions.

1. Introduction

Heart failure (HF) affects 26 million adults worldwide, with 5.7 million adults diagnosed in the USA [1]. Heart failure has one of the highest disease burdens and acute decompensated heart failure (ADHF) is the leading cause of hospitalization in the USA [2]. Although there have been significant improvements in medical therapy, HF admission rates did not change significantly from 2000 to 2010 [2]. In the OPTIMIZE-HF registry (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) the post-discharge readmission rate was approximately 30% within 60–90 days and the median length of hospital stay (LOS) was 4 days [3]. Hospital management of ADHF has advanced significantly in the past few decades, with the use of diuresis as a mainstay of treatment. Many studies have confirmed the safety and efficacy of loop diuretics but the starting dose in ADHF remains an area that lacks evidence. American College of Cardiology Foundation and American Heart Association 2013 Heart Failure guidelines recommend starting with a higher or equal to home dose of loop diuretics in ADHF admissions [4]. In the DOSE trial

which is the largest prospective randomized double-blind trial assessing diuretic strategies in heart failure, Felker et al concluded that there is no significant difference in global assessment of symptoms or change in renal function when loop diuretics used at a high-dose were compared with low-dose [5]. Patients with heart failure require higher loop diuretic dose to achieve sodium excretion [6]. Diuretic resistance has multiple studied mechanisms and it was suggested to have a different threshold for the same patient in the ADHF state [7]. The role of high-loop diuretic dose early in management of heart failure is unclear and some reports suggested its association with adverse outcomes [8]. The aim of this study is to assess the effect of first-24-hours loop diuretic dose on hospital length of stay (LOS). We hypothesized that a higher hospital/home diuretic dose ratio in the first 24 h of admission will be associated with a shorter LOS.

2. Method

Patients discharged from Danbury Hospital (a tertiary center and community teaching hospital in western

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Connecticut) in the 15 months between February 2015 and April 2016 with a primary diagnosis of ADHF were included in the study. Systematic chart review was performed using the hospital electronic medical records and the pharmacy medication administration systems. Patients involved in the study were identified based on their discharge or death primary diagnosis. Exclusion criteria were admission to the Intensive Care Unit (ICU) at any point during hospitalization, patients < 18 years of age or patients with end stage renal disease (ESRD). Patients were divided into three categories based on the loop diuretics dose administered in the first 24 h to home dose ratio. Group 1 included patients who were not taking any loop diuretics at home but were given any dose in the first 24 h. Group 2 received a hospital dose less than their home dose. Group 3 received greater than or equal to their home dose. The primary outcome was the LOS. Secondary outcomes were 30 day readmission rates, in-hospital mortality, percentage of weight loss, and incidence of acute kidney injury.

Patient demographics, vital signs, laboratory results, hospitalization outcomes, and medications administered in the first 24 h of admission and during hospitalization were collected (Table 1). For the primary analysis, loop diuretic intravenous dose in the first 24 h was compared to regular home oral dose prior to admission to calculate the hospital/home loop diuretics dose ratio. Length of hospital stay was counted by calendar days and by hours starting from the first medical contact in the Emergency Department until the departure of the patient. Ejection fraction data were collected from the most recent echocardiography performed during the same hospitalization or during a prior to hospitalization. Mortality and 30-day readmission data were generated automatically from electronic medical records. EFFECT score (Heart Failure Mortality Prediction Score) was calculated for all patients to control for severity of illness. The EFFECT score is comprised of age, respiratory rate, systolic blood pressure, blood

urea nitrogen (BUN), serum sodium level, presence of cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hepatic cirrhosis, cancer, or hemoglobin < 10 g/dl [9]. Development of acute kidney injury (AKI) was defined by increase in serum creatinine of ≥ 0.3 mg/dL or > 50% developing over < 48 h [10]. Percentage of weight loss was calculated by comparing discharge to admission weight.

Clinical characteristics of patients with roughly normal distributions such as body mass index (BMI) and systolic blood pressure (SBP) were summarized by mean and standard deviation (SD). Other features with skewed distributions, such as serum BUN and creatinine, were summarized by median and, first (Q1) and third quartile (Q3). Categorical variables were presented by percentages and frequencies. We employed Kruskal–Wallis testing to compare the percentages of weight loss, difference of admission and discharge creatinine and other quantitative features between different dose groups. T-test was used for comparing the LOS between sub-groups in group 3. For the pairwise comparisons between different dose groups, Tukey–Kramer procedure was used for quantitative features, and Pearson's chi-square test was used for categorical contingency tables. To assess the correlation between dose ratio and LOS, we used Spearman rank correlation, and partial correlation was considered while controlling for EFFECT score. Pearson's chi-square test was used to assess the association between dose group and renal function. The p-values shown below were before adjusting for multiple hypotheses control and the level of significance was 0.05. The statistical analyses were performed by R programming language, and 'ppcor' package was used.

3. Results

Of 650 eligible patients, 609 were included in the data analysis after excluding 41 patients (24 patients were admitted to the ICU at any point during

Table 1. Patients demographics.

	Group 1	Group 2	Group 3	P-value
Median age (Q1, Q3)	83 (73, 88)	79 (68, 89)	84 (75, 89)	0.212
Mean body mass index (SD)	29.32 (12.112)	28.71 (6.564)	29.28 (7.900)	0.669
Mean systolic blood pressure by mmhg (SD)	150.6 (28.851)	124.5 (27.083)	140.5 (27.275)	< 0.0001
Mean EFFECT score (SD)	89.82 (28.315)	108.5 (30.468)	98.31 (25.814)	< 0.0001
Mean serum sodium by mEq/L (SD)	137.4 (15.248)	136 (17.593)	138.8 (7.168)	0.153
Median serum BUN by mg/dl (Q1,Q3)	22 (18, 30.25)	33.5 (19.5, 54.75)	27 (20, 39.5)	< 0.0002
Median serum creatinine by mg/dl (Q1,Q3)	1.01 (0.79, 1.40)	1.43 (1.0425, 1.74)	1.17 (0.915, 1.63)	< 0.0003
Median serum BNP by pg/ml (Q1,Q3)	666.5 (344.25, 1116)	642 (370, 1427.5)	604 (326.25, 1138.5)	0.805
Median ejection fraction % (Q1, Q3)	57.5 (32.5, 62.5)	57.5 (32.5, 62.5)	57.5 (32.5, 62.5)	0.892
Use of Digoxin hospital use. (%)	8.716%	16.364%	13.690%	0.1306
Use of ACEI/ARB (%)	59.174%	29.091%	47.917%	< 0.0002
Use of BB (%)	82.110%	74.545%	88.095%	0.01422
Use of Mineralocorticoid antagonist (%)	5.505%	23.636%	10.119%	< 0.0003
Use of Thiazides (%)	4.128%	9.091%	4.762%	0.3159

Group 1: patients who were not taking any loop diuretics at home but were given any dose in the first 24 h. Group 2: patients who received a hospital dose less than their home dose.
Group 3: patients who received greater than or equal to their home dose.
All medications use was during hospitalization.
Q1: Quartile 1, Q3: Quartile 3, BUN: Blood Urea Nitrogen, BNP: B-type Natriuretic Peptide.

hospitalization, 12 patients had ESRD and 5 patients did not have complete data available). The most common loop diuretic used at home and in the hospital was furosemide. For patients who did not use furosemide but used other loop diuretics, we used the dose conversion rates from Table 2 [11]. Baseline characteristics presented in Table 1 show; some differences among the groups. For example group 2 had statistically significantly lower systolic blood pressure (mean 124.5 mm/hg), higher EFFECT score (mean of 108.5) and higher serum creatinine (median 1.43 mg/dl). Baseline criteria were not statistically significantly different among the groups in age, BMI, ejection fraction and BNP levels.

Among the groups there was a numerical difference in LOS by days but this was not statistically significant ($p = 0.081$, mean LOS for group 1, 2 and 3 was 4.9, 5.7 and 5 days, respectively- Table 3). In group 1 there was no statistically significant correlation between loop diuretics dose and LOS. In groups 2 and 3 there was no statistically significant correlation between loop diuretic dose ratio and LOS. The lack of correlation remained in all groups even after controlling for severity of illness using the EFFECT score (Table 4). Group 3 was further divided into two subgroups: group 3A (195 patients) received less than 2.5 times their home dose and group 3B (141 patients) received greater than or equal to 2.5X home dose. There was no statistically significant difference in LOS between group 3A and 3B ($p = 0.462$).

Thirty day readmission rate in our study was 19.7% in the study sample, which was comparable to the 2012 national average of 30-day readmission rate of 19% [12], and there was no statistically

significant difference among the three dose groups $p = 0.313$ (Table 5). In the study sample, in-hospital mortality was 2.5% and there was a statistically significant difference among the groups ($p = 0.045$). Group 2 had the highest in-hospital mortality rate among the groups (7.3%). Percentage of weight loss was statistically significantly different among the groups ($p = 0.045$), but for pairwise comparison there was no statistically significant difference (p-values for comparing group 1 with 2, group 2 with 3, and group 1 with 3 were 0.189, 0.898, and 0.060 respectively). Finally, the incidence of AKI was higher in group 2 and there was a statistically significant difference among the groups ($p = 0.0084$).

4. Discussion

Diuretic use in ADHF is strongly recommended by professional societies that are concerned with HF management to improve symptoms [4,13]. Loop diuretics produce a more intense and shorter diuresis than thiazides. The mechanism of action of loop diuretics in heart failure is inhibition of Na+-K+-2Cl− reabsorptive pump in the thick ascending limb of the loop of Henle [6]. Loop diuretic efficacy may be affected by many factors, primarily bioavailability (Table 2) and loop diuretic resistance [14]. Loop diuretic resistance and adaptation are both heavily discussed in the recent literature and although there are many suggested mechanisms and risk factors, there is a gap between our understanding of the pathophysiology and fundamental clinical trials that provide guidance to therapy [7,15]. Loop diuretics are organic anions that circulate bound to proteins (> 90%), limiting their volumes of distribution. Loop diuretics require secretion across proximal tubular cells, through organic anion transporters and the multidrug resistance–associated protein 4. Genetic deletion of organic anion transporters in mice leads to diuretic resistance. While gut edema and low duodenal blood flow do not typically affect oral loop diuretics bioavailability they slow absorption, thereby reducing peak plasma levels and also contributing to diuretic resistance [7]. Identified risk factors for resistance are hypotension, hyponatremia, lower kidney function, severe HF symptoms, and severe cardiac dysfunction as identified by Cleland et al [6] In order to

Table 2. Conversion of loop diuretics.

Loop diuretic	Bioavailability*	Equivalent Dosing*
Bumetanide IV	100%	1 mg
Bumetanide Oral	80–90%	1 mg
Torsemide Oral	80–100%	20 mg
Furosemide IV	100%	20 mg
Furosemide Oral	~ 50% (varies)	40 mg
Ethacrynic Acid IV	100%	50 mg
Ethacrynate Sodium Oral	100%	50 mg

*Bioavailability and dose response depends on disease state and prior exposure to diuretics.
Table is obtained from Society of Critical Care Medicine, The Intensive Care Professionals.
http://www.learnicu.org/Lists/Web%20Contents/Attachments/9640/DrugShortageAlert,%2011.15.12.pdf

Table 3. Length of hospital stay (LOS) and Loop diuretics dose in different groups.

Dose group	Summary	LOS in Days	LOS in hours	Home dose	Hospital dose	Hospital & home dose ratio	Effect score
Group 1 (218 patients)	Mean	4.87	118.90		81.61		89.82
	SD	4.05	96.56		47.20		28.32
	Range	(0, 41)	(12.77, 70.60)		(0, 280)		(18, 206)
Group 2 (55 patients)	Mean	5.69	138.80	171.8	88.18	0.51	108.5
	SD	3.47	82.99	130.07	67.002	0.27	30.47
	Range	(2, 18)	(40.90, 432.70)	(20, 800)	(0, 240)	(0, 0.92)	(36, 191)
Group 3 (336 patients)	Mean	4.98	120.80	56.31	114.5	2.77	98.31
	SD	3.24	78.10	46.05	64.43	2.01	25.81
	Range	(1, 28)	(17.93, 79.60)	(5, 320)	(20, 400)	(1, 16)	(19, 192)

Table 4. Primary Outcome (Hospital dose ratio to LOS).

	LOS in days*		LOS in days (controlling for EFFECT score)	
	Correlation coefficient	P-value	Partial correlation	P-value
Group 2	−0.020	0.886	−0.046	0.742
Group 3	−0.003	0.963	−0.005	0.933

* Among the groups, there was numerical difference in the length of hospital stay by days, yet this was not statistically significant (p-value = 0.081, mean LOS for Group 1, 2 and 3 was 4.9 days, 5.7 days and 5 days respectively).

Table 5. Secondary outcomes.

	Group 1 (N = 218)	Group 2 (N = 55)	Group 3 (N = 336)	Total (N = 609)	P-value
30-day readmission	43 (19.7%)	15 (27.3%)	62 (18.5%)	120 (19.7%)	0.312
In-hospital mortality	3 (1.8%)	4 (7.3%)	8 (2.4%)	15 (2.5%)	0.045[a]
% of weight loss (Mean)	4.079%	2.519%	3.247%	3.474%	0.045[b]
Mean difference between admission and discharge creatinine	−0.045	0.129	−0.021	−0.017	0.009[c]

[a]Between group 1 and 2, there was significant association between the dose group and in-hospital mortality, and the p-value was 0.0303. Comparing group 2 with 3 or 1 with 3, there was no significant association between the dose group and in-hospital mortality, and the p-values were 0.074 and 0.548 respectively.
[b]Pairwise comparison there was no statistically significant difference with p-values for comparing group 1 with 2, group 2 with 3, and group 1 with 3 were 0.189, 0.898, and 0.060 respectively
[c]There was significant difference of difference of admin & DC creatinine between group 1 and group 2 (p-value 0.006), and between group 2 and group 3 (p-value 0.031). There was no significant difference of difference of admin & DC creatinine between group 1 and group 3 (p-value 0.483).

control for loop diuretic resistance in our retrospective observational study, we divided our patient population into the three aforementioned groups based on hospital/home diuretic dose ratio in 24 h rather than absolute diuretic doses. We also compared outcomes among all groups and in each group separately, to avoid comparing a patient who requires a high-dose loop diuretic at home with a diuretic naive patient. ICU patients were excluded because many other factors affect their diuretic dose and the first 24 h diuretic dose plays a less important role in their hospital stay. In the DOSE trial, patients were randomized into four groups based upon 2 by 2 factorial design (low- versus high-loop diuretic dose and continuous infusion versus bolus doses). One of the secondary outcomes was length of hospital stay that was not statistically significantly different among the groups. In the DOSE trial there was an improvement of symptoms in all groups that was the highest at 72 hr which was the end of intervention time after which physicians had to decide the diuretic dose [5]. Patients with heart failure require higher loop diuretic dose to achieve sodium excretion but the role of first-24-hour dose on outcomes is unclear and was not previously studied [16]. In our hypothesis generating study, the analysis did not show any correlation between the hospital/home dose diuretic ratio and LOS among the groups.

Loop diuretic use in patients with heart failure may result in a significant decrease in glomerular filtration rate in some patients, presumably due to the renin–angiotensin–aldosterone system and sympathetic nervous system activation with related changes in renal blood flow and glomerular filtration pressure. Some patients with ADHF may have improvement in renal function with diuretic therapy [17,18]. Some observational studies suggest worse outcomes in patients who received higher doses of

loop diuretics in ADHF [8,15,19,20]. In fact, in the pooled analysis of our sample summing all groups together, higher loop diuretic dose (not the hospital/home dose ratio) was associated with longer length of hospital stay (correlation coefficient 0.117 and p-value = 0.004), and this correlation remained statistically significant after adjusting for EFFECT score (partial correlation coefficient 0.106 and p-value = 0.009). This finding may be explained by the fact that patients with severe fluid retention will need higher diuretic dose and longer duration for diuresis. Theoretically, this can be controlled in a randomized trial by considering the weight difference of patients from their dry weight before randomization. Among the groups, AKI and in-hospital mortality were higher in group 2 although they received lower loop diuretic dose ratio than group 3. This finding can be explained by more impaired baseline kidney function and higher EFFECT score of group 2 which make them the sickest group. We should exercise caution in interpreting any data comparing group 2 to the other groups due to significant baseline differences. In any future heart failure studies, a marker of patients' sickness level should be assessed and used for randomization to avoid an inaccurate assumption concerning patients in group 2.

Our study has limitations. First our study is retrospective and while we controlled for severity of illness using EFFECT score, there may be other confounding factors which we could not control. While the prevalence of chronic kidney disease, diabetes mellitus and coronary artery disease was significantly different among groups, other factors like age, BMI, serum sodium and ejection fraction were not statistically significantly different. Second, more patients may need to be included in the study for the results to exhibit statistical difference between groups, but our

analysis did not suggest any monotone association. Lastly, first 24 h diuretic dose or dose ratio of the loop diuretics may not play a major role in ADHF management possibly because acute heart failure is a very dynamic process, making it hard to standardize the treatment over a short period of time. It is still vital to illustrate the lack of observed correlation to enable the design of a large randomized clinical trial.

In conclusion, there was no correlation between the diuretic dose ratio and length of hospital stay in patients with ADHF in our retrospective observational study. Additional randomized controlled trials need to be conducted in order to provide more evidence and guidance for dosing loop diuretics in ADHF admissions. Until then the standardization of dosing of loop diuretics in ADHF remains elusive.

Acknowledgments

Disclosure statement

No potential conflict of interest was reported by the authors.

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