SHORT COMMUNICATION

Association of early administration of furosemide with improved oxygenation in patients with acute heart failure

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Abstract

Aims   Optimal pharmacological treatment for chronic heart failure has been established. However, treatments that can improve the prognosis of acute heart failure (AHF) are controversial. Although intravenous diuretics may be one optimal treatment option, little evidence has shown the effect of early administration of diuretics on clinical outcomes in patients with AHF. The aim of this study was to evaluate the association between door-to-furosemide (D2F) time, improved oxygenation, and in-hospital mortality in patients hospitalized for AHF.

Methods and results   We screened 494 patients hospitalized for AHF in Miyazaki Prefectural Nobeoka Hospital. AHF patients who were treated with intravenous furosemide within 24 h of arrival at the hospital were included in this study. D2F time was defined as the time from patient arrival at the hospital to the first intravenous dose of furosemide. The early administration group was defined as those with D2F time ≤60 min, whereas the non-early group was defined as those with D2F time >60 min. The primary outcome was the rate of improved oxygenation at Day 1. The secondary outcomes were in-hospital mortality and cardiac death.
There were 219 patients treated with the first intravenous dose of furosemide within 24 h analysed after the exclusion of 275 patients. The median D2F time was 55 min (interquartile range: 30–120 min) in the final cohort. The early administration group included 121 patients (55.3%). The rate of improved oxygenation was higher in the early group than the non-early group [median 16.7% (interquartile range: 0.0–40.0) vs. 0.0% (0.0–20.6), respectively, $P < 0.001$]. During the study period, there were six patients (5.0%) with in-hospital mortality in the early group and nine patients (9.2%) in the non-early group ($P = 0.218$). Cardiac death was observed less frequently in the early group than in the non-early group, but without statistical significance (3.3% and 9.2%, respectively) ($P = 0.067$). The univariable logistic regression analyses showed that early administration of furosemide was associated with improved oxygenation [odds ratio (OR): 2.26; 95% confidence interval (CI): 1.31–3.91; $P = 0.004$], but not with in-hospital mortality (OR: 0.52; 95% CI: 0.18–1.50; $P = 0.225$) or cardiac death (OR: 0.34; 95% CI: 0.10–1.13; $P = 0.079$). In multivariable analyses adjusted for risk score or relevant variables, early administration of furosemide was consistently associated with improvement of oxygenation.

Conclusions   The present study showed that in AHF patients, the early administration of furosemide was associated with improved oxygenation.

Background

Optimal treatment for chronic heart failure (HF) has been established, but it is not clear which treatment strategy will improve the prognosis of acute HF (AHF).[1] Intravenous (IV) furosemide is one of the emergency treatments for AHF. A multicentre observational study showed that the early administration of IV furosemide was associated with lower in-hospital mortality[2] and the current HF guideline in Japan recommends starting treatment as soon as possible.[3] A plausible mechanism of the effect of IV furosemide on the improvement of in-hospital mortality may be early relief of congestion; however, little evidence has shown the association of early administration of IV furosemide with improved oxygenation as the index of relief of congestion.

Aims

We investigated the association between door-to-furosemide (D2F) time, improved oxygenation, and in-hospital mortality in patients hospitalized for AHF.

Methods

We screened 494 patients hospitalized for AHF in Miyazaki Prefectural Nobeoka Hospital between 1 January 2015 and 31 March 2018. AHF patients who were treated with IV furosemide within 24 h of arrival at the hospital were included in this study. D2F time was defined as the time from patient arrival at the hospital to the first IV furosemide, which was calculated from the medical record. AHF was diagnosed by experienced cardiologists based on the Framingham criteria.[4]

Exclusion criteria were (i) re-admission for AHF; (ii) missing data of left ventricular ejection fraction (LVEF); (iii) missing data of B-type natriuretic peptide (BNP); (iv) treated without IV furosemide; (v) haemodialysis; (vi) emergency coronary angiography; (vii) pre-hospital IV furosemide; (viii) D2F time $\geq$24 h. According to a previous study,[2] 60 min was used as a cut-off for D2F time. The early administration group was defined as patients with D2F time $\leq$60 min, whereas the non-early group was defined as those with D2F time >60 min.

The primary outcome was the rate of improved oxygenation at Day 1, which was calculated as $\{100*[(\text{Day-0 FiO}_2) - (\text{Day-1 FiO}_2)]/(\text{Day-0 FiO}_2)\}$. FiO_2 was reduced by the attending physician according to the current HF guideline in

Figure 1 Study flow chart. This chart shows the enrolment criteria and the flow of patients with acute heart failure who were divided into two groups according to door-to-furosemide time. BNP, B-type natriuretic peptide; D2F, door-to-furosemide; HF, heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
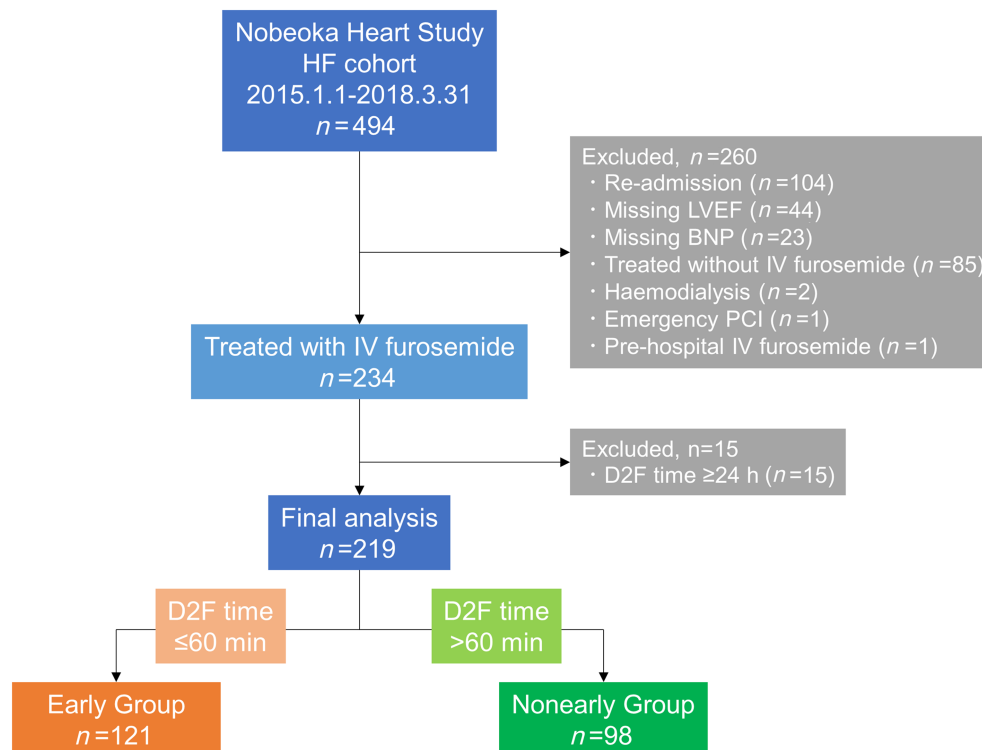
Table 1 Baseline characteristics

	Early group n = 121	Non-early group n = 98	P value
Age, years	84 (77, 88)	83 (72, 88)	0.430
Male, n (%)	61 (50.4)	50 (51.0)	0.929
Arrived by ambulance, n (%)	104 (86.0)	66 (67.3)	0.001
Systolic blood pressure, mmHg	160 (140, 183)	140 (116, 172)	<0.001
>140 mmHg, n (%)	88 (72.7)	46 (46.9)	
100–140 mmHg, n (%)	31 (25.6)	42 (42.9)	
<100 mmHg, n (%)	2 (1.7)	10 (10.2)	
Diastolic blood pressure, mmHg	96 (84, 111)	84 (64, 100)	<0.001
Heart rate, beats/min	102 (85, 122)	98 (80, 114)	0.193
NYHA at admission			0.032
III, n (%)	20 (16.5)	28 (28.6)	
IV, n (%)	101 (83.5)	70 (71.4)	
LVEF, %	44.0 (33.5, 53.0)	46.5 (34.8, 57.0)	0.195
HFrEF, n (%)	46 (38.0)	34 (34.7)	
HFmrEF, n (%)	35 (28.9)	19 (19.4)	
HFpEF, n (%)	40 (33.1)	45 (45.9)	
GWTG-HF score	39 (34, 45)	41 (37, 48)	0.015
Current or ex-smoker, n (%)	82 (67.8)	69 (70.4)	0.675
Hypertension, n (%)	94 (77.7)	74 (75.5)	0.705
Dyslipidaemia, n (%)	24 (19.8)	24 (24.5)	0.408
Diabetes mellitus, n (%)	58 (47.9)	44 (44.9)	0.654
Coronary artery disease, n (%)	39 (32.2)	27 (27.6)	0.453
Chronic obstructive pulmonary disease, n (%)	3 (2.5)	3 (3.1)	>0.99
Atrial fibrillation, n (%)	49 (40.5)	39 (39.8)	0.916
Chronic kidney disease, n (%)	89 (73.6)	72 (73.5)	0.989
Pneumonia at admission, n (%)	13 (10.7)	23 (23.5)	0.012
Acute biliary tract infection at admission, n (%)	0 (0.0)	1 (1.0)	0.447
Medication			
Furosemide dosage, median (IQR)	20 (20, 20)	20 (20, 20)	0.074
5 mg, n (%)	0 (0)	1 (1.0)	
10 mg, n (%)	7 (5.8)	12 (12.2)	
20 mg, n (%)	111 (91.7)	83 (84.7)	
40 mg, n (%)	3 (2.5)	1 (1.0)	
60 mg, n (%)	0 (0)	1 (1.0)	
IV nitrates, n (%)	53 (43.8)	18 (18.4)	<0.001
IV hANP, n (%)	67 (55.4)	44 (44.9)	0.123
ACE inhibitor/ARB, n (%)	117 (96.7)	91 (92.9)	0.226
Aldosterone blocker, n (%)	22 (18.2)	22 (22.4)	0.433
Beta-blocker, n (%)	56 (46.3)	39 (39.8)	0.336
Diuretics, n (%)	109 (90.1)	92 (93.9)	0.309
Laboratory data			
Hgb, g/dL	12.3 (10.2, 13.6)	11.5 (10.3, 13.4)	0.602
LDL-C, mg/dL	99 (80, 118)	86 (73, 109)	0.009
BUN, mg/dL	22.0 (17.1, 31.9)	22.2 (17.2, 34.5)	0.536
Creatinine, mg/dL	1.10 (0.80, 1.53)	1.01 (0.88, 1.43)	0.914
Glucose, mg/dL	159 (128, 231)	142 (110, 172)	<0.001
HgbA1c, %	5.9 (5.6, 6.4)	6.0 (5.7, 6.6)	0.353
Na, mEq/L	140 (137, 143)	140 (136, 142)	0.423
CRP, mg/dL	0.46 (0.13, 2.09)	0.82 (0.24, 4.62)	0.010
BNP, pg/mL	615.0 (308.8, 1396.2)	500.8 (343.9, 1038.3)	0.395
Length of hospital stay, days	17 (12, 23)	17 (12, 23)	0.860

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; GWTG-HF, Get With The Guidelines-Heart Failure; hANP, human atrial natriuretic peptide; HFmrEF, HF with mid-range EF; HFpEF, HF with preserved EF; HFrEF, heart failure with reduced EF; Hgb, haemoglobin; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Values are median (interquartile range) or n (%).

Japan.[3] Oxygen administration methods were nose cannula (FiO_2 = 0.21 + oxygen flow rate * 0.04), oxygen mask (FiO_2 = oxygen flow rate * 0.08), reservoir mask (FiO_2 = oxygen flow rate * 0.1), and non-invasive positive pressure ventilation and intubation. The secondary outcomes were all-cause in-hospital mortality and cardiac death. Cardiac death was defined as death due to HF, acute myocardial infarction, stroke, or sudden cardiac death.

Group comparisons were performed with the Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables, as appropriate. Logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for early furosemide administration in the improved oxygenation at Day 1 as the binary outcome divided by the median and in-hospital mortality. The Get With the Guidelines-Heart Failure (GWTG-HF) risk score,

which is based on race, age, systolic blood pressure, heart rate, blood urea nitrogen, sodium levels, and the presence of chronic obstructive pulmonary disease,[5] was calculated for each patient. This score has been used for predicting in-hospital mortality rate for AHF and is well-validated in Japanese patients with AHF.[6] The GWTG-HF risk score, LVEF, BNP, New York Heart Association (NYHA), and clinical scenarios were used as covariates in multivariable analysis. A two-tailed P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY, USA).

Results

Among 494 patients admitted for AHF during the study period, there were 219 patients treated with the first dose of IV furosemide within 24 h analysed after the exclusion of 275 patients. Excluded patients fell under the following categories: (i) re-admission ($n = 104$); (ii) missing data of LVEF ($n = 44$); (iii) missing data of BNP ($n = 23$); (iv) treated without IV furosemide ($n = 85$); (v) haemodialysis ($n = 2$); (vi) emergency percutaneous coronary intervention ($n = 1$); (vii) prehospital IV furosemide ($n = 1$); (viii) D2F time $\geq$24 h ($n = 15$) (Figure 1). We divided the 219 included patients into two groups based on D2F time with a cut-off of 60 min. The median D2F time was 55 min (interquartile range: 30–120 min) in the final cohort. The early administration group included 121 patients (55.3%), and the non-early group included 98 (44.7%). Baseline characteristics for the groups are shown in Table 1. The early group was more likely to arrive by ambulance and had higher systolic and diastolic blood pressure. Moreover, the early group had a higher NYHA class; however, the median GWTG-HF risk score in the early group was lower

Figure 2 Primary and secondary outcomes. Improved oxygenation rates at Day 1 in both groups are shown in left box-and-whisker plots; lines within the boxes represent median values; the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively; and the upper and lower bars outside the boxes represent maximum and minimum values within 1.5 times the interquartile range from the 75th and 25th percentile, respectively. Right bar graph shows all-cause death and cardiac death.
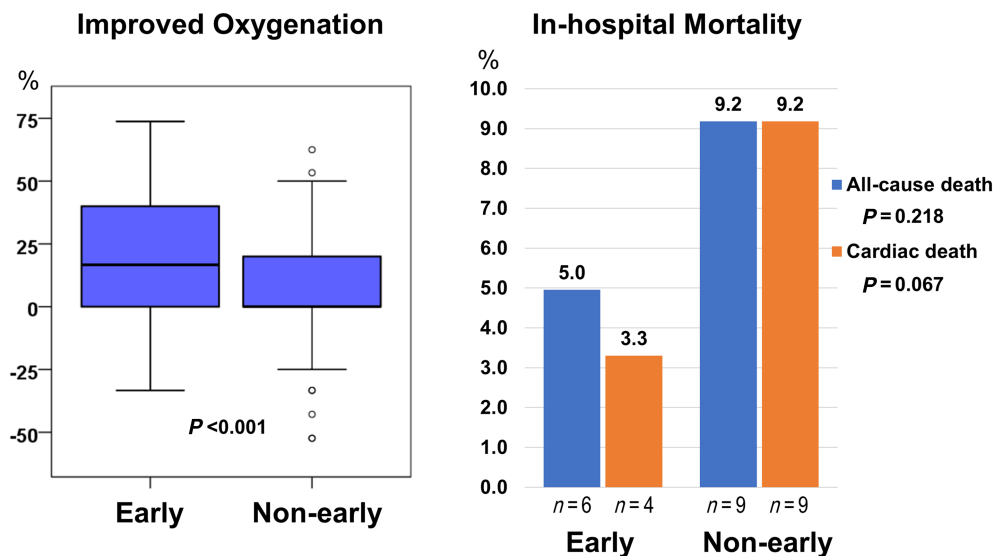

Table 2 Univariable and multivariable logistic regression analysis for improved oxygenation and in-hospital mortality

	Improved oxygenation			In-hospital death			In-hospital cardiac death		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Early administration	2.26	1.31, 3.91	0.004	0.52	0.18, 1.50	0.225	0.34	0.10, 1.13	0.079
+GWTG-HF	2.17	1.24, 3.77	0.006	0.62	0.21, 1.84	0.386	0.39	0.12, 1.35	0.137
+GWTG-HF + LVEF	2.15	1.24, 3.75	0.007	0.61	0.20, 1.83	0.380	—	—	—
+GWTG-HF + BNP	2.13	1.22, 3.71	0.008	0.60	0.20, 1.81	0.361	—	—	—
+GWTG-HF + NYHA	1.92	1.08, 3.42	0.026	0.55	0.18, 1.66	0.286	—	—	—
+GWTG-HF + pneumonia	2.21	1.26, 3.89	0.006	0.70	0.23, 2.13	0.530	—	—	—
+GWTG-HF + CRP	2.22	1.25, 3.93	0.006	0.71	0.23, 2.23	0.555	—	—	—
+GWTG-HF + eGFR + Hgb	2.16	1.23, 3.78	0.007	—	—	—	—	—	—

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR indicates odds ratio. Other abbreviation in Table 1.

than that in the non-early group. In the non-early group, there were 23 (23.5%) patients who had pneumonia and 1 (1.0%) who had acute biliary tract infection at admission, whereas there were only 13 (10.7%) who had pneumonia in the early group. Significant group differences in baseline laboratory markers were found for low-density lipoprotein cholesterol, glucose, and C-reactive protein. There was no significant difference in furosemide dosage between the two groups. However, there was a higher proportion of IV nitrate administration in the early group than in the non-early group. *Figure 2* shows the comparisons between the early and non-early groups for improvement in oxygenation and in-hospital mortality. The rate of improved oxygenation was higher in the early group than in the non-early group [median 16.7% (interquartile range: 0.0–40.0) vs. 0.0 (0.0–20.6), respectively, *P* < 0.001]. During the study period, there were six patients (5.0%) with all-cause death in the early group and nine patients (9.2%) in the non-early group (*P* = 0.218, *Figure 2*). Cardiac death was observed less frequently in the early group than in the non-early group, but without statistical significance (3.3% and 9.2%, respectively) (*P* = 0.067). *Table 2* shows the results of logistic regression analysis for improved oxygenation and in-hospital mortality. The univariable logistic regression analyses show that early administration of furosemide was associated with improved oxygenation (OR: 2.26; 95% CI: 1.31–3.91; *P* = 0.004) but not with in-hospital mortality (OR: 0.52; 95% CI: 0.18–1.50; P = 0.225). In multivariable analyses adjusted for GWTG-HF risk score, LVEF, BNP, NYHA, comorbid pneumonia at admission, C-reactive protein, eGFR, or haemoglobin, early administration of furosemide was associated with improved oxygenation.

Conclusions

The present study showed that, in AHF patients, the early administration of furosemide was associated with improved oxygenation and tended to be associated with a better in-hospital outcome, although this was not significant. Although the REALITY-AHF study showed that IV furosemide within 60 min was associated with a better in-hospital outcome in AHF patients,[2] the Korean AHF registry showed that D2F time was not associated with in-hospital or post-discharge death.[7] This discrepancy between the two prospective multicentre cohort studies might be due to differences in patient characteristics, such as age, LVEF, or D2F time, and the nature of observational study design.

Although there is no evidence of an obvious mechanism underlying the association between shorter D2F and better in-hospital survival, a randomized clinical trial may provide insight into how early treatment can prevent worsening myocardial and other organ damage in acute phase of AHF, followed by improving in-hospital outcomes. The RELAX-AHF study and a substudy showed that early treatment of AHF with serelaxin was associated with dyspnoea improvement, prevention of increased high-sensitivity troponin in the acute phase, and better survival.[8,9] This insight suggests potential mechanisms by which early administration with furosemide could prevent myocardial and organ damage via early relief of congestion and improved hypoxia, thereby improving in-hospital mortality. For the nature of this retrospective observational study, we could not evaluate biomarkers of myocardial and organ damage and determine the causal relationship between early administration of furosemide and improved oxygenation. In addition, urinary flow may be an important factor that can explain how early administration of furosemide improves oxygenation; however, no data on urinary flow were collected in this study. Similar to the results of prospective studies,[2,7] there was no significant difference in the length of hospitalization. Plausible explanations for this lack of difference are as follows: (i) difference in the number of in-hospital deaths with shorter hospital stays between the two groups, (ii) presence of factors that have a greater impact on length of stay than early administration of furosemide, and (iii) that length of hospitalization could not be evaluated as a clinical outcome of AHF in the Japanese inpatient medical care system. Future studies are needed to confirm the association of D2F time with improved oxygenation and decreased mortality and to investigate the underlying mechanisms.

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