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Research Article / Araştırma Makalesi

Nitrate and Diuretic Treatments in Acute Heart Failure within 30 Minutes: A Cross Sectional Study in Emergency Department

Akut Kalp Yetersizliğinde İlk 30 Dakika İçinde Nitrat ve Diüretik Tedavileri: Acil Serviste Kesitsel Bir Çalışma

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Abstract

Diuretics and nitrates form the cornerstone of emergency treatment, and more recently, some observational studies have highlighted the importance of the concept of 'time' in the treatment of Acute Heart Failure (AHF). We aimed to investigate clinical manifestations, phenotypes, and outcomes of patients with AHF and required early diuretics and nitrates administration. Patients who presented to the ED with signs and symptoms of acute heart failure were included in the study. The clinical features of the early (30 minutes and less) and delayed (over 30 minutes) treatment groups were evaluated according to the duration of diuretic and nitrate treatment. The median age of the 719 patients was 73 years [66–80 IQR] and 395 (54.9%) were male. Furosemide treatment was administered to 682 (94.9%) patients, and 537 (74.7%) patients received glycerol trinitrate treatment. In-hospital mortality rates were high in patients who received early treatments of both furosemide and nitrate (OR: 5.802, 95% CI: 1.885–17.831, p = 0.001 and OR: 5.229, 95% CI: 1.355–20.115, p = 0.013, respectively). The 3-month mortality rates were also high in patients who received early furosemide treatment (OR: 1.864, 95% CI: 1.078–3.223, p = 0.026). Patients who were started diuretics and nitrates in the early period (<30 min) had shorter stays in the ED. In-hospital mortality was higher in early treatment group.
Keywords: heart failure, furosemide, nitrates, emergency department

Özet

Akut Kalp Yetmezliğinin (AKY) tedavisinde diüretikler ve nitratlar, acil tedavinin temel taşını oluşturur ve yakın zamanlarda, bazı gözlemsel çalışmalar, 'zaman' kavramının önemini vurgulamıştır. AKY bulunan, erken diüretik ve nitrat uygulaması gerektiren hastaların klinik belirtilerini, fenotiplerini ve sonuçlarını araştırmayı amaçladık. Acil servise akut kalp yetmezliği belirti ve bulguları ile başvuran hastalar çalışmaya dahil edildi. Erken (30 dakika ve altı) ve gecikmeli (30 dakika üzeri) tedavi gruplarının klinik özellikleri diüretik ve nitrat tedavisinin süresine göre değerlendirildi. 719 hastanın medyan yaşı 73 idi [66-80 IQR] ve 395'i (%54.9) erkekti. 682 (%94,9) hastaya furosemid tedavisi, 537 (%74,7) hastaya gliserol trinitrat tedavisi verildi. Hem furosemid hem de nitratın erken tedavisini alan hastalarda hastane içi ölüm oranları yüksekti (OR: 5.802, %95 GA: 1.885-17.831, p = 0.001 ve OR: 5.229, %95 GA: 1.355–20.115, p = 0.013, sırasıyla). Erken furosemid tedavisi alan hastalarda 3 aylık mortalite oranları da yüksekti (OR: 1.864, %95 GA: 1.078–3.223, p = 0.026). Erken dönemde (<30 dk) diüretik ve nitrat başlanan hastaların acil serviste kalış süreleri daha kısaydı. Hastane içi mortalite erken tedavi grubunda daha yüksekti.
Anahtar Kelimeler: kalp yetersizliği, furosemid, nitratlar, acil servis

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1. Introduction

Acute heart failure (AHF) is a life-threatening condition highly associated with morbidity and mortality. It is also one of the leading causes of hospitalizations in subjects aged >65 years and is associated with high mortality and rehospitalization rates and represents a significant economic burden on the healthcare system. In-hospital mortality ranges from 4% to 10%. Post-discharge 1-year mortality is reported to be 25-30% with up to more than 45% deaths or readmission rates1. The majority of patients with AHF initially present to the emergency department (ED). Furthermore, early diagnosis of AHF in the ED and prompt initiation of appropriate treatment strategy may influence clinical outcomes2–4. In patients with AHF, diuretics and nitrates form the cornerstone of treatment, and more recently, some observational studies have highlighted the importance of the concept of 'time' in the treatment of AHF. Although the management of acute coronary syndrome is similar for almost every patient, a single treatment approach or a fixed treatment program and timing do not seem appropriate for every AHF patients. Most patients with AHF present with worsening signs and symptoms of congestion, but only a minority of patients with low cardiac output findings. However, precipitating factors, underlying heart disease, clinical characteristics, and comorbidities may differ greatly in patients presenting with similar clinical picture and also, may effect physician's treatment approaches5,6. Although early initiation of diuretics in AHF treatment has been recommended, the appropriate timing, patient management, and optimal practices are still unclear and data on nitrates are not available.

In this study, we aimed to examine the clinical manifestations, and outcomes of patients who presented to the ED with AHF and required time interval to treatment ≤30 min diuretics and nitrates administration.

2. Methods

This is a cross sectional and observational study. It included patients aged ≥18 who presented to the ED of a tertiary university hospital between October 2015, and September 2016; were diagnosed with de novo heart failure (HF) and/or acutely decompensated HF (ADHF), and for whom treatment was recommended (Figure 1). The study was conducted with the approval of the local ethics committee (date: October 27, 2015; number: 56). Signed informed consent was obtained from the patients who participated in the study or from their relatives if they were unconscious. Patients aged <18, those with trauma, pregnant women, patients with known HF who presented to the emergency department for reasons other than HF complaints and symptoms, chronic renal failure (CRF) without urine output, N-terminal proBNP (NT-proBNP) levels <300 pg/mL and those who (or whose relatives) did not give their consent were excluded from the study.

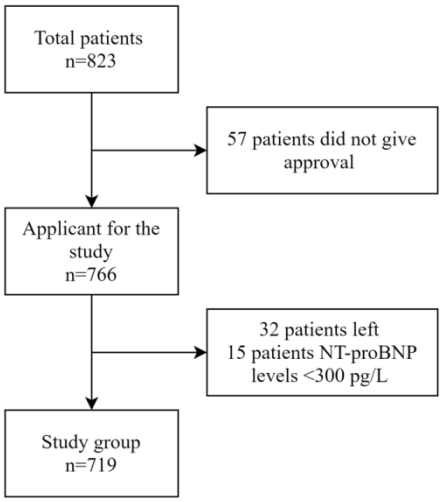

Figure 1. Flow chart of the patients participating in the study.

We recorded information from the patients regarding demographic data, comorbidities, medications, vital signs, the presence of typical signs and symptoms of HF, bedside echocardiography, chest X-ray, electrocardiography and laboratory findings, treatments and interventions performed in the ED, ED outcome (discharge/intensive care admission/hospitalization/death), and the duration of stay in the ED, intensive care unit, and hospital.

One or both nitrate or furosemide added to treatment if indicated by clinical findings. The time of treatment initiation (door-to-furosemide time and door-to-nitrate time) were recorded. No recommendations were made to the healthcare team during the diagnosis and treatment stages because of the nature of study. Patients with a time interval to treatment ≤30 min were assigned to the "early" treatment group and those with a difference of >30 min were assigned to the "delayed" treatment group. The primary outcome was ED visit that require IV therapy, re-hospitalization, and all-cause mortality in the following 3 months. The secondary outcome was to evaluate clinical factors causing a delay in administering diuretic and nitrate treatments.

During follow-up, patients were contacted via phone-call at 90th day. Presentations to the ED due to HF; hospitalizations due to HF; and the cause and date of death, were recorded.

Statistical Analysis

Continuous data were given data that do not fit into normal distribution were given as Median [25.-75. interquartile range], categorical data were given as a percentage (%). We used Shapiro Wilk's test to determine if the data fit into a normal distribution, Mann-Whitney U test is used when two groups did not. Cross-tables were analyzed with Pearson Chi-Square and Fisher Exact Chi-Square tests. Logistical regression analysis was used to determine risk factors. We used the IBM SPSS Statistics 21.0 program (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) to run the analyses.

3. Results

De novo HF was diagnosed in 373 (51.9%) patients and ADHF in 346 (48.1%) patients. The median age of the 719 patients was 73 years [66–80 IQR]. Of the patients, 395 (54.9%) were male and 324 (45.1%) were female. The median age was 72 years [65–78 IQR] for men, whereas it was 73 years [68–82 IQR] for women ($p < 0.001$). The median age of de novo patients was 73 years [64–80], and it was 73 years [66–77] in the ADHF group. The number of female patients was 189 (50.7%) among the de novo HF patients and 135 (39.0%) among the ADHF patients ($p = 0.002$). Based on the medical history, there were 516 (71.8%) patients with hypertension, 260 (36.2%) patients with diabetes mellitus, 119 (16.6%) patients with chronic kidney disease (CKD), 180 (25.0%) patients with chronic obstructive pulmonary disease, and 305 (42.4%) patients with coronary artery disease (CAD). The number of active smokers was 201 (28.0%). 512 (71.2%) patients' systolic blood pressure was higher than 140 mmHg.

The most common symptom was dyspnea in 714 (99.3%) patients followed by orthopnea in 688 (95.7%) patients, fatigue in 476 (66.2%) patients, palpitations in 353 (49.1%) patients, paroxysmal nocturnal dyspnea in 341 (47.4%) patients, and increased swelling in the legs and body in 249 (34.6%) patients.

Nitrate treatment was started earlier in patients with a history of CAD [odds ratio (OR): 1.568, 95% confidence interval (CI): 1.071–2.294, $p = 0.020$]. Although there was no statistically significant difference, furosemide and nitrate treatments were started delayed in cases with de novo HF so that it could be clinically significant (50.5% vs. 54.6%, $p = 0.337$; 48.8% vs. 58.1%, $p = 0.055$, respectively). In the evaluation of the vital parameters, it was observed that both systolic blood pressure and diastolic blood pressure were higher in patients in whom treatment with diuretics and nitrates were initiated in the early period ($p < 0.001$ in both groups). Increased heart rate was found to be statistically significant in the early treatment groups for both furosemide and nitrate ($p =$

0.037 and p = 0.001). In addition, oxygen saturation was lower and respiratory rates were higher in the early treatment group (Table 1).

While the left ventricular EF (LVEF) was determined to be 30.0 [20.0–50.0] % in the entire patient group, 407 (56.6%) of patients had HFrEF, 118 patients (16.4%) had HFmrEF, and 194 patients (27.0%) had HFpEF.

Table 1. Baseline Characteristics of Study Patients

	Furosemide Group (n=682)			Nitrate Group (n=537)		
	Early 0-30 minutes (n=499)	**Delayed >30 minutes (n=183)**	**p**	**Early 0-30 minutes (n=389)**	**Delayed >30 minutes (n=148)**	**p**
Age, years [IQR]	73 [65-79]	73 [67-80]	0.238	74 [66-80]	73 [68-80]	0.458
Female, *n(%)*	221 (44.3%)	87 (47.5%)	0.450	167 (42.9%)	72 (48.6%)	0.234
De novo, *n(%)*	252 (50.5%)	100 (54.6%)	0.337	190 (48.8%)	86 (58.1%)	0.055
Comorbidities, *n(%)*						
HT	357 (71.5%)	138 (75.4%)	0.316	282 (72.5%)	114 (77.0%)	0.286
DM	181 (36.3%)	72 (39.3%)	0.462	151 (38.8%)	43 (42.6%)	0.428
CRF	86 (17.2%)	25 (13.7%)	0.263	67 (17.2%)	20 (13.5%)	0.297
COPD	134 (26.9%)	41 (22.4%)	0.238	105 (27.0%)	37 (25.0%)	0.640
CAD	298 (59.7%)	100 (54.6%)	0.234	240 (61.7%)	75 (50.7%)	**0.020**
AF	98 (19.6%)	33 (18.0%)	0.637	75 (19.3%)	22 (14.9%)	0.235
Smoker	142 (28.5%)	48 (26.2%)	0.565	109 (28.0%)	34 (23.0%)	0.237
Medication, *n(%)*						
Furosemide	251 (50.3%)	86 (47.0%)	0.444	198 (50.9%)	65 (43.9%)	0.148
Spironolactone	90 (18.0%)	29 (15.8%)	0.505	66 (17.0%)	23 (15.5%)	0.691
Nitrate	61 (12.2%)	23 (12.6%)	0.904	49 (12.6%)	19 (12.8%)	0.940
ACEI	119 (23.8%)	37 (20.2%)	0.317	98 (25.2%)	30 (20.3%)	0.232
ARB	86 (17.2%)	36 (19.7%)	0.462	71 (18.3%)	27 (18.2%)	0.998
Vitals [IQR]						
SBP, *mmHg*	150 [140-170]	140 [120-160]	**<0.001**	160 [140-170]	150 [130-160]	**<0.001**
DBP, *mmHg*	90 [80-100]	80 [80-90]	**<0.001**	90 [90-100]	90 [80-98]	**<0.001**
Heart rate, *bpm*	100 [85-117]	95 [80-115]	**0.037**	100 [86.5-120]	94.5 [80.5-112]	**0.001**
SpO2, *%*	89 [85-92]	90 [88-93]	**<0.001**	89 [85-91.5]	90 [88-92]	**<0.001**
Respiratory rate	28 [24-32]	24 [22-32]	**0.002**	28 [24-32]	24 [22-32]	**0.001**

IQR: Interquartile range, HT: Hypertension, DM: Diabetes mellitus, CRF: Chronic renal failure, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blockers, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SpO2: Oxygen saturation

The evaluation of laboratory parameters, additional treatments administered, and interventions performed in the ED according to whether they were administered or performed early or delayed are provided in Table 2. In the furosemide group, oxygen therapy was given at a higher rate in patients whose treatment was started early (OR: 1.966, 95% CI: 1.130–3.420, p = 0.016). In patients who received early furosemide treatment, nitrates were also started early (OR: 1.496, 95% CI: 1.010–2.218, p = 0.045), and in those receiving early nitrate treatment, furosemide was also started early; however, no significant difference was found (p = 0.05). Patients underwent noninvazive mechanical ventilation were more likely to be included in the early treatment group for both furosemide and nitrate (OR: 4.588, 95% CI: 2.112–9.953, p < 0.001 and OR: 2.769, 95% CI: 1.397–5.479, p = 0.002, respectively). ED and hospital outcomes regarding treatment times were shown on Table 3.

Table 2. Echocardiographic findings, laboratory parameters, chest x-ray findings, and ED treatment

	Furosemide Group (n=682)			Nitrate Group (n=537)		
	Early 0-30 minutes (n=499)	**Delayed >30 minutes (n=183)**	**p**	**Early 0-30 minutes (n=389)**	**Delayed >30 minutes (n=148)**	**p**
LVEF % [IQR]	35 [20-50]	30 [20-50]	0.425	35 [20-50]	35 [20-50]	0.814
HFrEF, *n(%)*	273 (54.7%)	107 (58.5%)	0.712	215 (55.3%)	80 (54.1%)	0.961
HFmrEF, *n(%)*	85 (17.0%)	29 (15.8%)		69 (17.7%)	27 (18.2%)	
HFpEF, *n(%)*	141 (28.3%)	47 (25.7%)		105 (27.0%)	41 (27.7%)	
Laboratory parameters, [IQR]						
pH	7.40 [7.35-7.45]	7.41 [7.36-7.45]	0.084	7.40 [7.35-7.44]	7.41 [7.36-7.45]	0.369
Lactate, *mmol/L*	1.9 [1.3-2.6]	1.6 [1.2-2.4]	**0.004**	1.7 [1.3-2.5]	1.6 [1.0-2.4]	**0.008**
Base excess, *mmol/L*	-3.1 [-6.2 - -1.0]	-3.0 [-5.2 - -0.4]	0.124	-3.1 [-6.0 - -0.9]	-3.0 [-5.3 - -0.9]	0.352
Hemoglobin, *g/dL*	12.0 [10.5-13.8]	11.7 [10.4-13.7]	0.196	12.1 [10.6-14.0]	11.7 [10.4-13.2]	**0.022**
Sodium, *mEq/L*	138.0 [134.0-140.0]	139.0 [135.0-141.0]	0.283	138.0 [135.0-140.0]	139.0 [134.0-141.0]	0.914
Potassium, *mEq/L*	4.73 [4.30-5.10]	4.73 [4.35-5.20]	0.364	4.70 [4.28-5.20]	4.60 [4.30-5.08]	0.371
BUN, *mg/dL*	27.7 [18.3-43.4]	25.7 [18.5-44.5]	0.763	27.0 [18.2-41.0]	25.5 [18.3-42.8]	0.739
Creatinine, *mg/dL*	1.25 [0.95-1.68]	1.20 [0.94-1.63]	0.473	1.25 [0.95-1.67]	1.22 [0.91-1.65]	0.606
NT-proBNP, *pg/mL*	6860 [3058-15550]	7410 [3180-14856]	0.820	6823 [3091-15440]	6898 [2994-13508]	0.728
hs-Troponin T, *ng/L*	41.0 [22.0-77.0]	38.0 [23.0-70.0]	0.667	41.0 [21.0-75.0]	37.5 [24.3-63.8]	0.864
ED Treatment and interventions in hospital, *n(%)*						
Oxygen	465 (93.2%)	160 (87.4%)	**0.016**	368 (94.6%)	133 (89.9%)	**0.050**
Nitrate	401 (80.4%)	134 (73.2%)	**0.045**			-
Furosemide			-	388 (99.7%)	147 (99.3%)	0.476
Inotrope	15 (3.0%)	3 (1.6%)	0.425	N/A	N/A	-
NIMV	77 (15.4%)	7 (3.8%)	**<0.001**	65 (16.7%)	10 (6.8%)	**0.003**
Endotracheal intubation	7 (1.4%)	1 (0.5%)	0.689	6 (1.5%)	0 (0%)	0.195
Ultrafiltration	26 (5.2%)	4 (2.2%)	0.088	19 (4.9%)	3 (2.0%)	0.136
Coronary angiography	68 (13.6%)	28 (15.3%)	0.578	56 (14.4%)	21 (14.2%)	0.951

IQR: Interquartile range, LVEF: Left ventricular ejection fraction, HFrEF: Heart failure with reduced EF, HFmrEF: Heart failure with mildly reduced EF, HFpEF: Heart failure with preserved EF, BUN: Blood urea nitrogen, NIMV: Non-invasive mechanical ventilation

Table 3. Emergency and hospital outcomes regarding treatment times.

	Furosemide Group (n=682)			Nitrate Group (n=537)		
	Early 0-30 minutes (n=499)	**Delayed >30 minutes (n=183)**	**p**	**Early 0-30 minutes (n=389)**	**Delayed >30 minutes (n=148)**	**p**
Time in ED, *min*	274.0 [200.0-373.0]	330.0 [270.0-416.0]	**<0.001**	280.0 [200.0-374.5]	345.0 [275.0-450.0]	**<0.001**
Hospital admission, *n(%)*	335 (67.1%)	97 (53.0%)	**0.001**	258 (66.3%)	76 (51.4%)	**0.001**
ICU admission, *n(%)*	161 (32.3%)	46 (25.1%)	0.073	124 (31.9%)	33 (22.3%)	**0.029**
Time in hospital, *days*	6.0 [4.0-10.0]	6.0 [4.0-11.0]	0.828	7.0 [4.0-10.0]	6.0 [5.0-10.0]	0.338
90 days ED readmission, *n(%)*	206 (45.6%)	76 (42.9%)	0.550	166 (46.0%)	68 (47.6%)	0.750
90 days hospital admission,	215 (47.8%)	70 (39.5%)	0.062	174 (48.2%)	61 (42.7%)	0.261

n(%)						
In-hospital exitus, *n(%)*	44 (8.8%)	3 (1.6%)	**0.001**	26 (6.7%)	2 (1.4%)	**0.013**
90 days exitus, *n(%)*	80 (16.0%)	17 (9.3%)	**0.026**	53 (13.6%)	12 (8.1%)	0.080

ED: Emergency department, ICU: Intensive care unit

It was observed that patients who received early furosemide treatment were hospitalized at a high rate (OR: 1.811, 95% CI: 1.283–2.566, p < 0.001). On the other hand, both hospitalization and intensive care unit admission rates were high those receiving nitrate (OR: 1.866, 95% CI: 1.271–2.739, p = 0.001 and OR: 1.631, 95% CI: 1.050–2.531, p = 0.029, respectively). In-hospital mortality rates were high in patients who received early treatments of both furosemide and nitrate (OR: 5.802, 95% CI: 1.885–17.831, p = 0.001 and OR: 5.229, 95% CI: 1.355–20.115, p = 0.013, respectively). The 3-month mortality rates were also high in patients who received early furosemide treatment (OR: 1.864, 95% CI: 1.078–3.223, p = 0.026).

4. Discussion

Diuretics, which are the foundation of HF treatment, and vasodilator treatments that lead to symptomatic relief have been evaluated in many different7,8.The necessity of starting HF treatment in the early period has been defined in several guidelines. In recent years, studies on door-to-diuretic time have been performed, and these studies report that diuretic treatment initiated within a time of ≤60 min reduces the in-hospital mortality2. It has also been shown that treatment initiated at or before 90 min reduces the length of hospital stay and all-cause mortality9. In addition, it was reported in another study that diuretic treatment initiated at 60 min or before did not lead to significant differences in terms of clinical outcomes10. In our study, we evaluated patients who received treatment within and after 30 min, and we could not find any previous evaluations in the literature based on this time. Although there are remain questions regarding the use of glyceryl trinitrate in the acute treatment of HF, it has been observed that it is used in treatment because patients are usually hypertensive and there is a need to reduce the afterload1,11,12. Besides, the effect of individual patient profiles in heart failure on the timing of diuretic and nitrate therapy administered in the ED is not well defined.

In previous studies, when vital parameters were evaluated, systolic blood pressures, diastolic blood pressures, and heart rate were found to be high in patients receiving early treatment2,10. Approximately three quarters of patients hospitalized for AHF have a history of chronic HT and more than one half have an initial systolic blood pressure (SBP)>140 mmHg at the time of hospital admission13. In present study, approximately 75% of the patients had a diagnosis of HT and 71.2% of the patients had SBP>140 mmHg. Presence of a diagnosis of HT did not affect the timing of diuretic and/or nitrate therapy. However, it was observed that the blood pressure level at the time of admission to the ED was related to the timing of both diuretic and nitrate treatment. In addition, the prognostic effect of heart rate in AHF and its effect on treatment management in ED admission are still debate and unclear. In individuals with chronic HF, elevated resting HR was reported to be associated with increased risks of cardiovascular disease and mortality14. In the hyperacute phase of AHF, tachycardia is a mostly beneficial physiological compensatory response. In contrast to the predictive role of this parameter in chronic HF and clarity on rate control, the role of heart rate in AHF is much more controversial and the details of the relationship between the pathophysiology of AHF and HR are still unknown15. In our study, it was observed that the heart rate affects the timing of treatment at the time of admission to the ED, and the patient profile with a higher heart rate was treated with diuretic and nitrate therapy earlier. In a recent study, it was reported that simple combined admission measurement of SBP and heart rate predicted a higher risk for 1-year all-cause mortality in the elderly population hospitalized for the first time for AHF16.

Limitations

The present study also has some limitations. First, it is a single-center study. Second, the treatment was not administered in a randomized controlled manner, and it was an observational study. Third, although healthcare professionals treating the patients received similar training, treatment may have been delayed in patients with possibly atypical presentations.

5. Conclusion

According to our study, patients who were started on diuretics and nitrates in the early period (<30 min) had shorter stays in the ED and were hospitalized more. In-hospital mortality was higher in the early treatment group. Since the early treatment group consists of clinically more critical patients, there is a need for more such studies and definitive clinical guidelines

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