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CLINICAL STUDY

Impact of prehospital IV furosemide or nitrate application on hospital outcome in acute heart failure patients

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ABSTRACT

OBJECTIVES: This study aims to evaluate the association between prehospital intravenous therapy and clinical outcomes in the patients with acute heart failure.

METHODS: We conducted a prospective, multicenter observational study of consecutive AHF patients. Univariate and logistic regression analysis were performed to determine association between prehospital furosemide or nitrates administration and hospital outcome (death, length of stay).

RESULTS: Data on a total of 1239 patients were processed. The mean age in the whole cohort was 71 ± 11.8 years with a gender distribution (M/F) of 634/605 patients. By prehospital treatment whole cohort was divided into 4 groups: F+ group with prehospital IV furosemide administration of 602 patients (48.6 %), F– group without prehospital IV furosemide administration of 637 patients (51.4 %), N+ group with prehospital IV nitrates administration of 110 patients (8.9 %) and N– group without IV nitrates administration of 1129 patients (91.1 %). Group of combined F+/N+ was not created. Ninety-four patients (7.6 %) died during the index hospitalization. Hospital mortality (p = 0.138) and length of stay (p = 0.101) did not differ in F+ vs F–. The patients with prehospital nitrates administration did not differ in mortality, but a shorter length of stay in univariate analysis (p = 0.03) was recorded. After adjusting for age, systolic BP and mode of referral to hospitalization, early IV furosemide usage nor nitrates showed no impact on hospital mortality and length of stay.

CONCLUSIONS: Prehospital treatment with IV furosemide or nitrates in AHF patients seemed to have no major impact on hospital mortality or length of hospitalization after adjustment for several cofounders *(Tab. 2, Ref. 16)*. Text in PDF *www.elis.sk*

KEY WORDS: acute heart failure, prehospital management, furosemide, nitrate.

Introduction

Heart failure (HF) is currently one of the most significant causes of mortality and morbidity, as well as one of the leading causes of hospitalization (1). The prevalence of HF among the adult population in developed countries is approximately 1–2 % and rises to more than 10 % at the age of 70 years (2). The estimated minimum incidence based on the number of hospitalizations for HF in Slovakia is at least 120.1/100,000 inhabitants (3). Despite advances in medical and device therapies for HF, admission rates remain high (4). In the prospective study of hospitalized patients with AHF (Acute Decompensated Heart Failure National Registry – ADHERE), in-hospital mortality was 4 %, in the EHFS II (Euro Heart Failure Survey II) it was 6.7 % (5, 6).

Acute heart failure (AHF) indicates a rapid onset or worsening of HF. Aggravating signs and symptoms of congestion are the main reasons, why the patients with AHF seek urgent medical care.

The current Recommendations of the European Society of Cardiology (ESC) have extensive support in evidence medicine for the treatment of chronic heart failure, while procedures in AHF management are most defined in class II, level of evidence B or C (2).

Accordingly, prehospital management is considered a critical component of care. The Recommendations for AHF formulated a "time to treatment" concept, which is based on the idea that rapid and effective decongestion in AHF can result in mortality and adverse events reduction (7).

The goal of the study was to analyse the data from the SLOVASeZ II and SLOVASeZ III Registries (3,8) focusing on prehospital treatment aimed to decongestion (diuretics, nitrates) and their impact on hospital mortality and the length of stay.

Patients and methods

This study was designed to analyse demographic and clinical characteristics of acute HF patients in the Slovak Republic through multicenter prospective surveys (SLOVASeZ – Slovak Acute Heart

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Tab. 1. Characteristics of patients included in the SLOVASeZ II and III study.

	Total	F+	F–	p	N+	N–	p
Number of patients (%)	1239	602(48.6)	637 (51.4)		110 (8.9)	1129 (91.1)	
Age, median years (IQR)	73 (64–81)	73 (65–81)	73 (64–81)	0.043	76 (67–81)	73 (64–81)	0.045
Gender, n male (%)	643 (51.0)	315 (52.3)	319 (50.1)	0.429	47 (42.7)	587 (52)	0.063
BMI median kg/m2 (IQR)	28.7 (25.4–32.9)	28.5 (25.2–32.5)	29.1 (25.7–33.2)	**0.032**	27.3 (25.1–32.1)	28.9 (25.5–32.9)	0.059
NYHA class IV n (%)	458 (37.0)	249(41.4)	209 (32.8)	**0.002**	67 (60.9)	391 (34.6)	< **0.001**
Primary HF etiology n (%):							
Coronary heart disease	532 (42.9)	256 (42.5)	276 (43.3)	0.775	56 (50.9)	476 (42.2)	0.076
Dilated cardiomyopathy	141 (11.4)	64 (10.6)	77 (12.1)	0.419	4 (3.6)	137 (12.1)	**0.007**
Arterial hypertension	181 (14.0)	98 (16.3)	83 (13.0)	0.105	23 (20.9)	158 (14.0)	0.050
Arrhythmia	97 (7.8)	44 (7.3)	53 (8.3)	0.508	3 (2.7)	94 (8.3)	**0.036**
Other	288 (24.0)	140 (23.3)	148 (23.3)	0.993	24 (21.9)	264 (23.4)	0.710
HF phenotype:							
Echocardiography available n (%)	956 (77.0)	465 (77.2)	491 (77.0)		88 (80.0)	868 (76.8)	
HFrEF	311 (25.0)	156 (25.9)	155 (24.3)	0.514	24 (21.8)	287 (25.4)	0.269
HFmrEF	296 (24.0)	150 (24.9)	146 (22.9)	0.399	37 (33.6)	259 (22.9)	**0.018**
HFpEF	349 (28.0)	159 (26.4)	190 (29.8)	0.148	27 (24.5)	322 (28.5)	0.234
Baseline HF medications:							
ACEI /ARB	767 (61.9)	372 (61.8)	395 (62.0)	0.487	83 (75.5)	684 (60.6)	< **0.001**
Beta-blocker	811 (65.5)	405 (67.3)	406 (63.7)	0.19	75 (68.2)	736 (65.2)	0.529
MRA	489 (39.4)	251 (41.6)	238 (37.4)	**0.021**	32 (29.1)	457 (40.5)	0.215
Furosemide	837 (67.6)	414 (68.8)	423 (66.4)	0.374	63 (57.3)	774 (68.6)	**0.016**
Hydrochlorothiazide	112 (9.0)	55 (9.1)	57 (8.9)	0.908	7 (6.4)	105 (9.3)	0.305
Past medical history n(%):							
CABG	69 (5.6)	35 (5.8)	34 (5.3)	0.715	7 (6.4)	62 (5.5)	0.703
Valvular heart disease	49 (4.0)	21 (3.5)	28 (4.4)	0.413	3 (2.7)	46 (4.1)	0.489
PKI	191 (15.4)	91 (15.1)	100 (15.7)	0.777	20 (18.2)	171 (15.1)	0.400
Diabetes mellitus	581 (47.0)	287 (47.7)	294 (46.2)	0.592	53 (48.2)	528 (46.8)	0.777
Atrial fibrillation	351 (28.3)	197 (53.8)	154 (54.8)	0.804	20 (42.6)	331 (55.2)	0.095
Chronic obstructive pulmonary disease	267 (21.5)	146 (24.3)	121 (19)	**0.024**	32 (29.1)	235 (20.8)	**0.044**
Cancer	164 (13.2)	88 (14.6)	76 (11.9)	0.163	18 (16.4)	146 (12.9)	0.311
Myocardial infarction	381 (30.8)	193 (32.1)	188 (29.5)	0.332	48 (43.6)	333 (29.5)	**0.002**
Peripheral arterial disease	194 (15.7)	109 (18.1)	85 (13.3)	**0.021**	17 (15.5)	177 (15.7)	0.951
Thyroid disease	96 (7.7)	49 (13.4)	47 (16.7)	0.236	3 (6.4)	93 (15.5)	0.090
Dyslipidaemia	663 (53.5)	335 (55.6)	328 (51.5)	0.143	70 (63.6)	593 (52.5)	0.026
Chronic kidney disease	588 (47.5)	305 (50.7)	283 (44.4)	**0.028**	51 (46.4)	537 (47.6)	0.810
Arterial hypertension	1091 (88.1)	531 (88.2)	560 (87.9)	0.873	106 (96.4)	985 (87.2)	**0.005**
Orthopnea at admission	497 (40.1)	280 (46.5)	217 (34.1)	< **0.001**	70 (63.6)	427 (37.8)	< **0.001**
Systolic blood pressure n (%):							
≤100 mmHg	99 (8.0)	33 (5.5)	66 (10.4)	**0.002**	2 (1.8)	97 (8.6)	**0.012**
100–40 mmHg	655 (52.0)	312 (51.8)	343 (53.4)	0.477	34 (30.9)	621 (55.0)	< **0.001**
≥140 mmHg	485 (39.0)	257 (42.7)	228 (35.8)	**0.013**	74 (67.3)	411 (36.4)	< **0.001**
Heart rate median, beats/minute (IQR)	88 (75–105)	90 (76–106)	86 (74–100)	0.325	90 (80–110)	87 (75–103)	0.457
Fast ambulance transport to the hospital n (%)	465 (37.5)	287 (47.7)	178 (27.9)	< **0.001**	87 (79.1)	378 (33.5)	< **0.001**
Other mode of referral n (%)	774 (65.0)	315 (52.3)	459 (72.1)	< **0.001**	23 (20.9)	751 (66.5)	< **0.001**
HF related hospitalisation within previous 12 months n (%)	368 (29.7)	177 (29.4)	191 (30.0)	0.823	26 (23.6)	342 (30.3)	0.145

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; BMI – body mass index; CABG – coronary artery bypass graft; F+ – intravenous furosemide within 12 hours before admission; F– without intravenouse furosemide within 12 hours before admission; HF – heart failure; HFrEF – heart failure with reduced ejection fraction; HFmrEF – heart failure with mildly reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction, CHF – chronic heart failure; MRA – mineralocorticoid receptor antagonist; N+ – intravenous nitrate within 12 hours before admission; N– – without intravenous nitrate 12 hours before admission NYHA – New York Heart Association Classification; PCI – percutaneous coronary intervention

Failure Registry II and III) with 1239 consecutive patients enrolled in 14 hospitals throughout Slovakia.

In the SLOVASeZ II registry, data collection took place during the months of April to June 2014, the SLOVASeZ III registry covered the months of September 2017 to March 2018 in 14 centers. The selection of centers was carried out in such a way as to represent all types of hospital practice from university hospitals to large regional hospitals and smaller district hospitals. Investigators were instructed to register consecutive patients over 18 years of age with de-novo HF or acute decompensated HF admitted to the hospital. All acute HF cases were confirmed by the local center investigator based on the clinical criteria, plasma natriuretic peptide and/or echocardiography following current ESC guideline recommendations (2). The patients with acute coronary syndromes were excluded. The data were recorded in electronic form and sent to the control center. The form contained 120 parameters in

10 categories. It was aimed to obtain data on demographic, clinical and laboratory characteristics of AHF patients, diagnostic procedures, therapy and in-hospital outcomes. Specific questions on prehospital pathway and treatment were included (8). For extensive description of the patient population (Tab. 1). To meet the goal of analysis, patients were divided according to whether they received prehospital IV furosemide (F+) or not (F–) and IV nitrates (N+) or not (N–). The time between hospital arrival and IV furosemide administration was not recorded, nor furosemide/nitrate dosage. Hospital mortality and the length of in-hospital stay were set as endpoints. Ethical approval for this project was granted by the Central Ethics and Medical Research Committee of National Cardiovascular Institute in Bratislava (Reference Number 8/14 for SLOVASeZ II and Reference Number 8/17 for SLOVASeZ III). All the participating patients gave informed consent to be included in the registry. The study was carried out in strict compliance with the Declaration of Helsinki principles.

The data are presented using descriptive statistics. Continuous data are presented as median and interquartile range and categorical data as absolute values and percentages. The χ^2 test and, where appropriate, Fisher's exact test were applied using SPSS Statistics (Version 25) to assess for any significant differences between the groups. Cases where data were missing or unavailable were excluded. A ρ value < 0.05 was taken as statistically significant. The magnitude of the association between prehospital IV furosemide and prehospital nitrates administration and outcomes was estimated using logistic regression and expressed as odds ratio with 95 % confidence interval. Variables were screened by univariate analysis and four selected variables with highest significance of potential bias were inserted in the multivariable logistic regression.

Results

The data on a total of 1239 patients admitted due to AHF were processed (592 patients from the SLOVASeZ II, 647 patients from the SLOVASeZ III). The mean age in the whole cohort was 71 ± 11.8 years with a gender distribution (male/female) of 643/596 patients (51.2/ 48.8 %). Fast ambulance transport to the hospital was recorded in 465 patients (37.5 %). The patients in the NYHA functional class III and IV together accounted for more than 92.3 % of the patients. Coronary heart disease observed in almost 43 % was the most common primary aetiology of HF in the whole cohort. Baseline characteristics are outlined in Table 1.

Orthopnea was the dominant symptom associated with more frequent diuretics and nitrates administration before admission. Systolic blood pressure (BP) values below 100 mmHg were reported in 99 patients (8 %). Systolic BP was above 100 mmHg in 1140 (92 %) patients, with values above 140 mmHg being present in almost 39 % of the total number of the patients. Treatment initiated 12 hours before hospitalization was predominantly represented by intravenous furosemide in 602 (48.6 %) patients and by intravenous nitrates in 110 (8.9 %) patients. Systolic BP was the most important clinical parameter associated with furosemide or nitrates administration. Intravenous nitrates or furosemide were given less frequently in the group with systolic BP less than 100mmHg (5.5 % vs 51.8 %, respectively; $\rho < 0.001$). The patients in the NYHA class IV classification were more likely to receive intravenous loop diuretics and/or nitrates respectively (see Table 1). Fast ambulance transport as a mode of referral to hospitalization was associated with more frequent parenteral treatment administration in both groups (furosemide and nitrates), for F+ 47.7 % vs 27.9 %, respectively; $\rho < 0.001$, for N+ 79.1 % vs 33.5 %, respectively; $\rho < 0.001$. According to univariate analysis, prehospital furosemide administration was not associated with difference in hospital mortality (OR 0.69; CI 0.46–1.07; $\rho = 0.101$). No association was found with the length of stay (OR 1.19; CI 0.95–1.49; $\rho = 0.138$). Hospital mortality was not different in the prehospital nitrates group, but shorter length of stay in univariate analysis ($p = 0.03$) was recorded (Tab. 2). Results of multiple logistic regression analysis after adjusting for age, systolic blood pressure and fast ambulance transport as a mode of referral are shown in the Table 2.

Tab. 2. Univariate and multiple logistic regression analysis of IV furosemide/nitrates administration and outcomes.

Univariate logistic regression analysis - prehospital furosemide*				
	OR	CI		p
		min	max	
Death	0.69	0.46	1.07	0.101
Length of stay**	1.19	0.95	1.49	0.138
Univariate logistic regression analysis – prehospital nitrates*				
	OR	CI		p
		min	Max	
Death	0.68	0.29	1.59	0.379
Length of stay**	0.64	0.42	0.97	0.036
Multiple logistic regression analysis - prehospital furosemide*				
	OR	CI		p
		min	max	
Death	0.67	0.42	1.54	0.089
Length of stay**	1.22	0.96	1.54	0.100
Multiple logistic regression analysis – prehospital nitrates*				
	OR	CI		p
		min	Max	
Death	0.67	0.27	1.61	0.371
Length of stay**	0.64	0.42	1.00	0.049

* adjustment: age – BP – fast ambulance transport as a mode of referral; CI – confidence interval; OR – odds ratio; other abbreviations as in Table 1. ** length of stay below median versus equal and above median of 8 days

Discussion

Acute HF indicates a rapid onset or worsening of HF. It is a potentially life-threatening condition that requires immediate evaluation and treatment. Hospitalization for HF marks a substantial crossroad for the patients, as greater than one-third will be rehospitalized or dead within 90 days post-discharge. For patients with chronic HF, who present with acute HF syndromes, it means their transition from an arena of well-established and life-saving evidence-based therapies to one where early pharmacological management has changed little over the last 40 years (9). Given

the pivotal role of congestion in HF, diuretics are a cornerstone of the therapy in heart failure (10). Meanwhile, its level of evidence is weak (level C) (2). This may reflect the common use of loop diuretics despite that there are still doubts about the benefits related to the early diuretic administration in the patients suffering from pulmonary congestion secondary to HF. As for acute coronary syndromes, the "time to treatment" concept was discussed in the patients with AHF (12). Unfortunately, data defining optimal diuretic timing and dose are incomplete. In the ADHERE-EM (Acute Decompensated Heart Failure Registry-emergency module), the administration of intravenous HF therapy was associated with a modest, but significant increase in the risk of in-hospital mortality and length of hospitalization (11).

Treatment started 12 hours before hospitalization was according our study predominantly represented by administration of intravenous loop diuretics (48.9 % of patients). Intravenous furosemide was given more frequently in the patients with higher blood pressure, with more expressed clinical manifestation and those transported to the hospital by fast ambulance.

After adjusting for age, systolic BP and fast ambulance transport to the hospital as a mode of referral to hospitalization, furosemide usage had no impact on hospital mortality and length of stay. Matsue et al reported a beneficial effect in lower in-hospital mortality of early IV furosemide administration in the Japanese cohort for those patients receiving IV furosemide within 60 minutes of emergency department arrival (12). Park et al failed to demonstrate benefits of early IV furosemide in the similar Korean cohort (13). In the secondary analysis of EAHFE (Epidemiology of Acute Heart Failure in Emergency Department Registry) – FAST FURO study, the authors did not find association between early IV furosemide and short-term mortality or length of hospitalization (14). However, more than half of the studied patients in the FAST FURO study were in NYHA class I and II, which are not typical patients requiring intravenous diuretic therapy. Most of the patients in our cohort were in the NYHA class III and IV and were more likely to receive intravenous loop diuretics and/or nitrates respectively. Intravenous vasodilators are the second most often used agents in the management of the patients with AHF, however there is lack of evidence confirming their beneficial effects. By their dual effect, they decrease venous tone to optimize preload and reduce arterial tone to decrease afterload (15). Due to lack of the evidence from randomized controlled trials, the routine use of nitrates, vasodilators respectively in AHF management is not universally accepted. Actually, in the newest ESC guidelines in the patients with AHF and systolic BP > 110 mmHg, intravenous vasodilators were downgraded to IIb recommendation (2). In our study, intravenous nitrates in prehospital setting were given in 8.9 % of AHF patients. It was 9 % of those, who were potentially eligible for nitrates administration. Similarly in the retrospective observational study ESC-HF Long Term Registry, only 6.8 % of the patients with systemic pressure above 110 mmHg were treated with vasodilators (16). There was no significant difference in hospital mortality comparing groups with and without prehospital nitrates administration. We noticed a trend to shortening of the hospitalization length in the patients with prehospital nitrates administration. Nitrates were used preferentially in orthopnoic patients with systolic BP ≥ 140 mmHg.

Conclusions

Prehospital treatment with IV furosemide or nitrates in AHF patients was not associated with changes in hospital mortality or length of hospitalization after adjustment for several cofounders. Our study, derived from well-defined group of AHF patients, supports an observation that in current clinical practice prehospital treatment with furosemide or nitrates has no impact on hospital outcome. It does mean that prehospital treatment in AHF is irrelevant or meaningless. It could mirror the fact that prehospital intravenous therapy is used predominantly in the patients with significant symptoms on one the hand, but generally a better prognosis on the other.

Limitations

The SLOVASeZ registry was conducted as prospective study of consecutive AHF patients with pre specified questions on prehospital patient management. As registry contains a potential of bias for evaluation treatment strategies despite adjustment on selected variables. Our data show the prehospital IV furosemide in general has no impact on hospitalization results, but time point of furosemide administration or dose used was not recorded. We also have no data on changes of clinical status or congestion F+ vs F– or N+ vs N– patients.

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