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Original research article

Increased dose of diuretics correlates with severity of heart failure and renal dysfunction and does not lead to reduction of mortality and rehospitalizations due to acute decompensation of heart failure; data from AHEAD registry

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ARTICLE INFO

Article history:

Received 19 September 2017

Accepted 29 September 2017

Available online xxx

Keywords:

Acute heart failure

Rehospitalization

ABSTRACT

Background: Diuretics are being used to reduce symptoms of congestion and fluid retention in heart failure patients but their effect has not been studied in randomized clinical trials. The data about positive or negative effect of loop diuretics depending on their dose is conflicting and controversial. The aim of this analysis is to evaluate whether the relatively small increase in the dose of furosemide can reduce the incidence of readmissions for acute heart failure decompensation and/or total mortality.

Methods and results: We evaluated a total of 1119 patients admitted for ADHF who were discharged from the hospital back home in a stable condition. All surviving patients were

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Please cite this article in press as: M. Pavlusova et al., Increased dose of diuretics correlates with severity of heart failure and renal dysfunction and does not lead to reduction of mortality and rehospitalizations due to acute decompensation of heart failure; data from AHEAD registry, Cor et Vasa (2017), <https://doi.org/10.1016/j.crvasa.2017.09.007>

AHEAD
Mortality
Diuretic
Furosemide.

followed up for at least two years. The primary endpoint was a combination of hospital readmissions for acute heart failure and overall mortality. The primary analysis showed significantly different characteristics and prognosis of patients who did not require any loop diuretic and those requiring furosemide dose >125 mg. Therefore, we compared a group of patients with low-dose furosemide (10–40 mg) with a group of patients with high-dose furosemide (41–125 mg) only. The higher dose of diuretics correlated well with disease severity (lower systolic blood pressure, more frequent chronic exertional dyspnea NYHA III, lower left ventricular ejection fraction, increased creatinine levels). Long-term mortality and the number of rehospitalizations were lower in the low-dose diuretic group ($p = 0.037$ and $p = 0.036$, respectively) but after adjustment using the propensity score matching the incidence of the primary endpoint was comparable in both groups.

Conclusion: The dose of a loop diuretic recommended to patients with acute heart failure at hospital discharge correlates well with the severity of heart failure. When comparing the groups of patients with a higher dose of furosemide (41–125 mg) and a lower dose of furosemide (10–40 mg) we found that after adjustment using propensity score matching the higher dose of loop diuretic had a neutral effect on the incidence of the composite endpoint of overall mortality and/or readmission for ADHF.

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Introduction

The prognosis of patients hospitalized with acute heart failure is substantially poor, in-hospital mortality rate ranges from 4% to 12.7% [1–4] and the observed annual mortality rate of an unselected population is almost 33% [5]. Chronic dyspnea, low functional capacity and repeated rehospitalizations for acute decompensation are among the factors that significantly impair the quality of life of patients with heart failure. Rehospitalizations also increase the cost of their treatment [6]. Diuretics effectively relieve symptoms of dyspnea and control fluid retention in heart failure [7]. Faris et al. showed that diuretic treatment in patients with chronic heart failure reduced the risk of disease progression and improved functional capacity [8]. A meta-analysis of small placebo-controlled trials showed a decrease in mortality and a reduction of the risk of rehospitalizations in patients treated with loop diuretics [8]. In clinical practice, the non-compliance of patients to diuretic therapy is responsible for at least 4% of readmissions for ADHF [9]. Furosemide eliminates free water and sodium from the body, causes venodilation by releasing prostaglandins and thereby reduces right atrial pressure and pulmonary capillary wedge pressure [9,10]. On the other hand, loop diuretics may activate the renin-angiotensin-aldosterone and sympathetic nervous systems which have been associated with the progression of heart failure [10,11]. Several studies have also demonstrated that high-dose loop diuretics, particularly furosemide, are associated with the increased risk of death, progression of heart failure and ADHF hospitalizations [12–16]. A recent work published by Pellicori et al. showed that the prescription of higher doses of diuretics identified patients with advanced heart failure and congestion but in a multivariate analysis including natriuretic peptides and echocardiographic signs of congestion the high dose of diuretics did not prove to be an independent predictor of mortality and rehospitalizations for acute heart failure [17]. One of the major limitations of these studies is that they included incomparable (unmatched) patients in their analyses – both

those patients without the need for chronic treatment with loop diuretics on one hand and the patients with diuretic resistance and the necessity to administer doses of furosemide >125 mg daily on the other hand. Considering these conflicting results, we have developed an analysis to evaluate whether a relatively higher dose of a loop diuretic in patients with heart failure can result in a reduction of readmissions for ADHF and total mortality (primary composite endpoint). The secondary objective was to assess whether the prescribed diuretic dose at discharge affects the number of readmissions for acute decompensation of heart failure and overall mortality.

Methods

The study protocol complied with the Declaration of Helsinki, and was approved by the Multicenter Ethics Committee of University Hospital Brno (Brno, Czech Republic). A written informed consent was obtained from all subjects to participate in the study.

Study population

The Acute Heart Failure Database (AHEAD) Network registry comprises consecutive patients from ten centers with 24-h Catheter Laboratory service and centralized care for patients with acute coronary syndromes, described previously as “AHEAD Main” [4], and from five regional centers without a Catheterization Laboratory. This subanalysis comprises strictly consecutive patients only from the two largest centers – The University Hospital Brno and The Frydek Mistek Hospital (the first one with a cathlab, the latter without a cathlab). The follow-up in these two sites includes not only information about all-cause mortality but also information about cardiovascular rehospitalizations (e.g. ADHF, acute coronary syndrome, stroke/transient ischemic attack, arrhythmias including unplanned implantations of PM/ICD/CRT, myocardial revascularization [percutaneous coronary intervention or

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