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Letter to the Editor · Open Access ·

Increased mortality in elderly heart failure patients receiving infusion of furosemide compared to elderly heart failure patients receiving bolus injection

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Heart failure (HF) is a condition of cardiac dysfunction and fluid overload. Neurohormonal activation via the renin-angiotensin-aldosterone system and the sympathetic nervous system are the pathophysiological cornerstones.[1] Furthermore, HF is a disorder widely associated with grave adverse outcomes and poor prognosis.[2] A loop diuretic is the fundamental drug used to prevent multiorgan failure and improve symptoms in these patients.[3] Noteworthy worries have been put forth concerning the risks and benefits of loop diuretics, particularly about the dosage and administration procedure.[4,5] Several observational studies have shown that static drug exposure is associated with increased mortality risk.[6–15] Loop diuretics administered as a continuous infusion have been thought to convey further benefits over bolus injections.[16] However, there is no consensus on whether loop diuretics administered intravenously as bolus injections or continuously as infusions are the better choice.[17] Several meta-analyses have been performed to try to clarify the issue.[17–21] They have shown support for administering furosemide as a continuous infusion rather than intermittent bolus injection for greater diuresis/urine volume[17–19,21] and a greater reduction in total body weight.[19–21] However, there was no benefit in terms of all-cause mortality.[17,21] The aim of our study was to investigate the hypothesis that there would be a difference in outcome when elderly patients with severe HF are treated with loop diuretics administered as a continuous infusion compared to loop diuretics administered as bolus injections.

This was a single-center study of 40 Caucasian men and women who were hospitalized to the internal medicine ward at Skåne University Hospital in Lund because of worsened symptoms of their HF. All patients were enrolled into the study during the period January through September 2018, were in NYHA class III and IV, mean age over eighty, and had several concomitant diseases. The patients were randomly divided into two groups with 20 patients in each; one group that received intravenous loop diuretics as bolus and the other group receiving intravenous continuous loop diuretics as infusion. A thorough investigation of all the patient's medical records during the time of hospitalization, re-hospitalizations within 30 days, and deaths within 90 days of discharge gave the relevant data to analyze. Exclusion criteria were malignancy-induced HF and chronic renal failure which required loop diuretics. The same loop diuretic was used for all patients (Furix 10 mg/mL, 4 mL ampulla; Takeda Pharma AB, Solna, Sweden). Bolus injections were given one or several times a day in total daily doses of between 20 to 100 mg furosemide. Continuous infusions were given typically between 4 to 10 hours a day at doses of 100 to 500 mg furosemide dissolved in 100 to 250 mL of Sodium Chloride 9% solution. Calculations for comparison between the two groups were done using the Student's *t*-test for continuous variables and the Pearson's chi-square test for dichotomous variables. Paired samples *t*-test was used when comparing in-group differences before and after intervention. Statistical significance was set at $P < 0.05$. Statistics were performed using the SPSS 25.0 statistical software (IBM SPSS Inc., Chicago, IL, USA).

The results are presented in Tables 1–3 and Figure 1. Overall, the baseline demographics were very similar between the two groups (Table 1) which demonstrated that the two groups were well matched. They were in their eighties, hade the same female to male gender distribution, and had the same weight to length composition. Notably, they were also in the same NYHA class, 55% to 60% NYHA class IV. Basic blood tests, HF medication, and concomitant diseases did not differ significantly. However, patients in the group receiving furosemide as continuous infusions had signifi-

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cantly lower systolic blood pressure ($P < 0.01$) at baseline. Since loop diuretic treatment has the ability to affect natriuretic peptides, weight, and renal function, these parameters were tested at both enrollment into the hospital and at discharge (Table 2). Generally, there were no significant differences in these parameters between the two groups. Furthermore, there was no significant change in variables from enrollment to discharge within the same group (Table 3). However, there was somewhat of a net reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) within both groups, but the reduction was not statistically significant.

The main finding of this study was that the mortality at three months after discharge from the hospital was significantly higher in the group of HF patients receiving furosemide as continuous infusions compared to the group receiving furosemide as intravenous bolus injections

Table 1. Basic demographic parameters.

Variable	Loop diuretic bolus injection		Loop diuretic continuous infusion		*P*-value
	n	Outcome	*n*	Outcome	
Demographics					
Age, yrs	20	84.6 ± 1.6	20	80.1 ± 2.6	0.15
Gende, female	20	12 (60%)	20	12 (60%)	N/A
BMI, kg/m^2	15	26.7 ± 1.2	15	25.1 ± 0.9	0.31
NYHA class IV	20	11 (55%)	20	12 (60%)	0.75
SBP, mm Hg	20	140 ± 6.7	20	116 ± 3.6	< 0.01
DBP, mm Hg	20	81.7 ± 3.4	20	73.0 ± 2.6	0.06
ECG QRS, ms	16	126 ± 7.7	18	131 ± 8.4	0.67
Laboratory					
Hemoglobin, g/L	19	125.9 ± 4.4	20	119.0 ± 4.6	0.29
Sodium, mmol/L	20	139.1 ± 1.0	20	137.1 ± 1.3	0.26
Potassium, mmol/L	20	4.4 ± 0.3	20	4.2 ± 0.1	0.61
TNT, ng/L	18	122.2 ± 39.0	19	85.7 ± 29.6	0.46
Glucose, mmol/L	20	9.0 ± 0.8	19	8.1 ± 0.6	0.36
CRP, mg/L	20	60.1 ± 21.5	20	18.1 ± 5.5	0.07
Drugs					
Total number	20	11.1 ± 0.9	20	10.4 ± 1.0	0.61
ACE/ARB	20	12 (60%)	20	8 (40%)	0.21
BB	20	17 (85%)	20	16 (80%)	0.68
MRA	20	7 (35%)	20	6 (30%)	0.74
Imdur	20	6 (30%)	20	3 (15%)	0.26
Warfarin	20	4 (20%)	20	9 (45%)	0.09
NOAC	20	9 (45%)	20	4 (20%)	0.09
Comorbidities					
IHD	20	13 (65%)	20	9 (45%)	0.20
Hypertension	20	6 (30%)	20	7 (35%)	0.74
Atrial fibrillation	20	9 (45%)	20	10 (50%)	0.75
Stroke/TIA	20	6 (30%)	20	4 (20%)	0.47
Diabetes	20	6 (30%)	20	5 (25%)	0.72
Renal failure	20	4 (20%)	20	5 (25%)	0.71
COPD/Asthma	20	7 (35%)	20	2 (10%)	0.06
Re-admissions after 30 days					
Total number	17	4 (24%)	15	6 (40%)	0.32

Data are presented as means ± SE or *n* (%). ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BB: beta-blockers; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DBP: diastolic blood pressure; ECG: electrocardiogram; IHD: ischemic heart disease; MRA: mineralocorticoid receptor antagonist; N/A: not applicable; NOAC: novel oral anticoagulants; NYHA: New York Heart Association Classification; SBP: systolic blood pressure; TIA: transient ischemic attack; TNT: troponin T.

Table 2. Follow-up variables at enrollment and discharge.

Variable	Loop diuretic bolus injection		Loop diuretic continuous infusion		*P*-value
	n	Outcome	*n*	Outcome	
NT-proBNP*, ng/L	20	9640 ± 22	20	15901 ± 30	0.10
NT-proBNP#, ng/L	20	7380 ± 17	20	12536 ± 24	0.09
Weight*, kg	20	73.7 ± 3.9	20	71.7 ± 3.5	0.71
Weight#, kg	18	73.5 ± 4.2	18	69.7 ± 3.3	0.48
Creatinine*, μmol/L	20	126.1 ± 12.2	20	141.1 ± 13.4	0.42
Creatinine#, μmol/L	20	126.2 ± 14.7	20	148.8 ± 17.1	0.32
eGFR*, mL/min per 1.73 m^2	20	39.5 ± 3.0	20	35.7 ± 3.3	0.40
eGFR#, mL/min per 1.73 m^2	20	39.6 ± 2.9	20	35.0 ± 3.7	0.33

Data are presented as means ± SE. *Refer to enrollment. #Refer to discharge. eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 3. Change within variables from enrollment to discharge.

Variable	*n*	Enrollment-discharge	*P*-value
NT-proBNP*, ng/L	20	2260 ± 17	0.21
NT-proBNP#, ng/L	20	3366 ± 21	0.14
Weight*, kg	20	1.14 ± 1.2	0.35
Weight#, kg	18	1.43 ± 1.2	0.25
Creatinine*, μmol/L	20	–0.10 ± 8.3	0.99
Creatinine#, μmol/L	20	–7.75 ± 8.3	0.36
eGFR*, mL/min per 1.73 m^2	20	–0.10 ± 1.7	0.95
eGFR#, mL/min per 1.73 m^2	20	0.75 ± 1.9	0.70

Data are presented as means ± SE. *Refer to loop diuretic bolus injection. #Refer to loop diuretic continuous infusion. eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide.

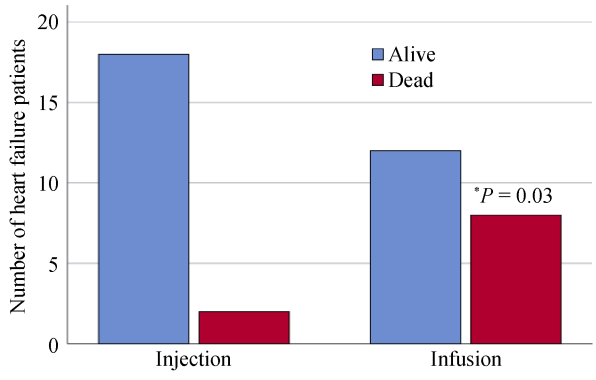

Figure 1. Mortality in heart failure patients (Bolus injection *vs.* Infusion of furosemide). Eight out of twenty patients in the infusion group were dead three months after discharge from the hospital, while two out of twenty patients in the bolus group were dead after three months. The difference between the two groups was significant, $P = 0.03$.

(Figure 1). Notably, at discharge (about one week later from enrollment), there was no significant difference in body weight in either treatment group, no change in the estimated glomerular filtration rate or in the serum creatinine levels. The treatment resulted in symptom relief and in a concomitant non-significant reduction in NT-proBNP (by 2260 ng/L in the bolus group and 3366 ng/L in the infusion group). Our results add important additional evidence to the current knowledge base for treating the elderly with severe HF.

The combined evidence up to date as depicted from the most recent meta-analyses published 2018 and 2019 have shown that there was no difference in mortality between the two modes of administering furosemide.[17,21] However, the interpretation of these meta-analyses is problematic. Overall, there were just too few deaths which makes any attempt of a certain conclusion leading the one way or the other impossible. Furthermore, the results from one meta-analysis[21] was weighted almost 75% on the study by Felker, *et al*.[22] which made the comparison a one-sided task. None the less, the trial by Felker, *et al*.[22] is important, since to the best of our knowledge, it is the largest of its kind. The trial showed that among patients with acute decompensated HF, there were no significant differences in patients' assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion. Also, all-cause mortality was the same.[22] Based on these findings, we must agree along with others that although providing important understandings into the

treatment of congestion, outcomes from these studies have largely been neutral leaving little influence on practice.[23]

It has previously been shown that continuous infusions reduce NT-proBNP levels to a greater extent than bolus injections in both decompensated HF and in acute HF with renal dysfunction.[22,24,25] On the contrary, we found presently that NT-proBNP in both groups of elderly severe HF patients were reduced to a similar extent by the two interventions. It is well known that increasing levels of NT-proBNP have been associated with increased mortality in HF patients[26] and reductions in natriuretic peptides have in general been associated with improved outcomes.[27] Considering this fact, we might have expected that meaningful decreases in NT-proBNP levels during the hospital stay would improve survival of the patients in the two groups. Yet, there were more deaths in the infusion group compared to the bolus group. The result could be interpreted in two main ways: (A) the infusion group could be somewhat frailer at baseline than the bolus group. In other words, the mode of administration of furosemide is merely a marker of disease severity. Even though infusion therapy decreased NT-proBNP levels to a similar extent as bolus therapy, the patients in the infusion group were worse off to start with inferring higher mortality risk regardless of treatment strategy. Without a doubt, persistent signs and symptoms of congestion at hospital discharge have been associated with high morbidity and mortality.[28,29] Also, we have previously shown that elderly patients with severe HF that were admitted to the hospital with high blood pressure were better off than HF patients that presented with low blood pressure.[30] Patients in the infusion group had significantly lower systolic blood pressure ($P < 0.01$) at baseline than the bolus group; and (B) alternatively, the infusion therapy, despite having favorable effects on NT-proBNP as did bolus therapy, conferred some additional detrimental effect because of the continuous administration procedure. Theoretically, however, the continuous infusion of furosemide seems superior to intermittent administration in some aspects.[16] Steady delivery of the drug to the nephron leads to more effective diuresis by preventing diuretic resistance, *i.e.*, rebound sodium retention and fluid reabsorption, and restricts potentially high-peak serum levels of furosemide that can increase toxicity when the drug is given as a bolus. Also, continuous infusion may decrease the fluctuations in intravascular volume. On the contrary, patients submitted to continuous infusion may be exposed to more persistent kidney damage, which promotes neuroendocrine overdrive, leading to increased tubulo-glomerular feedback.[24] Also, continuous furosemide administration as an infusion often restricts the patient to his/her hospital bed increasing the likelihood of a worsened circulation, orthostatic hypotension, pulmonary edema, atelectasis, pneumonia and the like. Indeed, we have previously shown that orthostatic blood pressure is associated with increased mortality in elderly patients with HF.[31] A thought would be that the way to administer furosemide might share aspects with those of nitric oxide drugs given as anti-anginal medication. Intermittent use preserves the efficacy while continuous administration reduces efficacy.

The concept of diuretic resistance[32] can work both in favor of and disfavor of continuous and intermittent administration of loop diuretics. "The braking phenomenon", a complex process that is due to changes in the structure and function of the kidney itself, triggering of the sympathetic nervous system, and alterations in several hormone pathways, could work in favor of intermittent administration. The efficacy of loop diuretics may weaken over time during long-term administration, as the body gradually adapts to their effects. "The post-diuretic effect", which refers to increased sodium retention after the loop diuretic has metabolically worn off, can favor better efficacy with continuous administration. "The rebound effect", which explains the occurrence of sodium retention when chronic loop diuretic use leads to compensatory increased distal nephron sodium reabsorption, favors intermittent administration.[33]

Furosemide acts on the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption.[34] The true pathophysiological pathways through which diuretics interact with the cardiovascular system and determine the prognosis of HF remain poorly investigated and understood.[11] However, there are several potential harmful pathophysiological effects of furosemide that could cause adverse reactions in the human body. Hypokalemia or hypomagnesemia are frequently observed adverse drug reactions to furosemide.[32] Potassium and magnesium abnormalities in patients with chronic HF could lead to potentially deleterious arrhythmogenic effects.[35] Furosemide can cause intravascular volume depletion, leading to hypotension, reduced glomerular filtration rate, and renal dysfunction; renal dysfunction being a well-established predictor of mortality in hospitalized patients with HF.[4]

Our study is unique in that it has examined very old patients, mean age over eighty. Almost all previous studies have included patients with a mean age between 50 and 70 years. This is important because it might be that the difference in mortality between bolus therapy and infusion therapy of loop diuretics only is apparent in the very elderly population. This fits well with the fact that the only other trial that also showed a clear significant increase in mortal-

ity (disfavoring continuous therapy) included patients with a mean age of around 80 years of age.[24,36] The mortality rate is high in the very elderly population and it is possible that this is important in order to have the power to detect a difference. Accordingly, we suggest that more trials be performed in the very elderly to examine if the association between lower mortality with bolus therapy is true. Like many of the other trials studying the administration of furosemide as bolus and infusion, our trial was a small, single-center study. Thus, we also suggest that more trials be performed with at least the size of Felker, *et al*.[22] However, management of elderly patients with severe HF is challenging and use of loop diuretics should be exercised with great care and only as symptomatic treatment.[37]

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