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ORIGINAL ARTICLE

Determinants of diuresis/natriuresis following ambulatory intravenous loop diuretics for worsening heart failure

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Abstract

Background The use of intravenous (IV) diuretics in an outpatient setting may represent an alternative to conventional hospitalization. Our objective was to identify factors associated with diuretic response during ambulatory IV diuretic sessions in a population of advanced heart failure with no therapeutic project and a frequent flyer profile.

Method All patients with 4-h IV diuretic sessions were analysed. An initial bolus followed a tailored protocol for continuous infusion based on the patient's baseline diuretic dose. Variables associated with diuresis and natriuresis following furosemide infusion were evaluated using mixed linear models.

Results Seventy-six patients (mean age 75.4 years; LVEF 42.7%; eGFR 40.7 mL/min/1.73 m^2) totalling 175 IV diuretic sessions were included. Mean diuresis was 1.0 L, natriuresis 92.6 mmol/L, and weight loss 610 grams. Baseline use of ACE inhibitors (+302 mL, $P = 0.0005$), eGFR (+160 mL per 10 mL/min/1.73 m^2 increase, $P < 0.0001$), and addition of thiazide during the diuretic session (+238 mL, $P = 0.0001$) were associated with higher diuresis. Prior percutaneous mitral valve repair or chronic thiazide treatment was associated with lower diuresis. Baseline use of ACE inhibitors (+10.83 mmol/L, $P = 0.018$) was associated with higher natriuresis. Worsening renal function (>3 mg/L increase from baseline) and dyskalaemia 48 h after these sessions were uncommon (respectively 11% and 15%).

Conclusions Ambulatory 4-h IV loop diuretic sessions induced a diuresis of approximately 1000 mL with a substantial sodium content, without causing significant complications. Addition of thiazide during the session increased diuresis and/or natriuresis, and could potentially be implemented to maximize the efficacy of ambulatory IV diuretic therapy.

Keywords Cardiovascular diseases; Heart failure; Diuretics; Ambulatory management; Worsening heart failure

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Introduction

In instances of significant heart failure (HF) decompensation with the need for intravenous depletion, management remains predominantly focused on conventional hospitalization, generating a cost estimated at 1% of total health expenses.[1] Repeated conventional hospitalizations are associated with iatrogenic risk and low quality of life.[2] Given the likelihood that, in the context of healthcare resource shortages,[3] only a minority of patients with worsening HF will ultimately be managed by means of conventional hospitalization, other options should be explored.

Ambulatory management of worsening HF in short (<4-h) structured day-hospital IV diuretics sessions was first reported by Buckley[4] in 2016. Until now, only a few studies have reported this approach,[5,6] primarily used in US centres. The ap-

proach to maximizing the efficacy of ambulatory IV diuretics sessions in a day-hospital setting has been scarcely studied, and less so in a European setting.

The present study aimed to (i) identify the factors associated with the response to diuretics (i.e., diuresis and natriuresis) and (ii) evaluate the biological tolerance.

Methods

Population

All consecutive patients treated with IV diuretics in day-hospital between July 2019 and May 2023 were studied. According to the department's protocol, patients with prior HF who experienced a congestive worsening episode identified through remote monitoring or during a consultation were eligible. Patients with de novo HF or low cardiac output episodes, whether associated with congestion or not, were excluded.

Diuretics protocol

All patients received a bolus of IV furosemide followed by 3 h continuous infusions at a fixed dose of 20 mg/h (60 mg for each patient) in order to maintain furosemide blood levels several hours after the bolus. The last hour consisted of diuresis measurement and observation. The dose used during IV sessions was adapted to the patients' background loop diuretics therapy in accordance with the protocol published by Buckley et al. (*Figure S1*).[4] The proportion of mega dose (>300 mg) was high (65%) as seen in *Table 2*. In the case of high baseline diuretic dose (>300 mg) or low diuresis 2 h after the IV bolus, a thiazide diuretic (25 mg hydrochlorothiazid per os) was added to overcome diuretic resistance. The dose was adjusted according to the patient's chronic loop diuretic regimen using the equivalence of 1 mg bumetanide to approximately 40 mg furosemide.

Vitals signs were assessed hourly during the diuretics session to ensure the effectiveness and tolerance of the intervention. Diuresis and natriuresis were evaluated during the day hospital stay before discharge for diuresis and 2 h after the diuretic injection for natriuresis. When severe congestion or persistent rest dyspnoea persisted after the IV diuretics session, particularly if the response to IV diuretics was considered insufficient, patients were directed to the standard hospitalization ward.

During the first week following the diuretics session, laboratory assessments were performed to verify the absence of severe worsening renal function or dyskalaemia. The protocol included a telephone interview with a HF nurse to confirm that they did not require another urgent IV diuretic session.

Outcomes

The primary endpoint of the study was total diuresis during the day-hospital IV diuretics session, with natriuresis as a secondary outcome.

Statistical analysis

All analyses were performed using R software (R version 4.1.2). The two-tailed significance level was set at $P < 0.05$. Continuous variables are described as mean ± standard deviation and categorical variables as frequency (percentage). The relationship between diuresis and natriuresis was assessed by calculating the linear correlation coefficient.

The predictors of diuresis and natriuresis were identified using a mixed linear model, adjusted for age and sex, with a random effect on patient number. A prediction model for each endpoint was then performed by backward selection with a significance level of 5%, beginning with the pre-selected variables, by forcing age and sex.

Among the potential predictors of diuresis/natriuresis, given that certain factors had missing data, multiple imputations with the R package mice[7] were performed by generating 100 imputed datasets and using the MID (Multiple Imputation then Deletion) strategy.[8] For the analyses (adjusted model and multivariable model), a model was constructed for each imputed dataset and the results pooled by applying Rubin's rules.[9]

Results

Mean patient age was 75.4 years with a LVEF of 42.7% (*Table 1*). The majority of patients were male (64%) and had a NYHA class III/IV (61%) (*Table 1*). Mean NT-proBNP was 10,266 pg/mL and eGFR 37.1 mL/min/1.73 m^2 at session admission.

During the IV sessions, a mean dose of 228 mg furosemide was administered, with a median of 260 mg. Approximately a third of the patients received a thiazide diuretic during the IV session. Mean diuresis was 1.0 L, median 0.9 L (0.6–1.3), mean natriuresis was 92.6 mmol/L, median 90.0 mmol (77–110), and mean weight loss was 610 g (*Table 2*). There was a good correlation between diuresis and natriuresis (r = 0.637). After the sessions, only 18% of patients required conventional hospitalization. The majority of sessions per patient were between 1 and 2, with a median of 1.9 per patient.

Variables associated with diuresis

Background medication was associated with diuresis during the IV session. The final multivariable model predicting diuresis (*Table 3*) identified high eGFR (beta = 0.160 for a 10 mL/

Table 1 Patient characteristics at baseline (N = 76 patients)

Clinical characteristics	
Age (years)	75.4 ± 12.5
Male sex	49 (64%)
Caucasian	65 (87%)
BMI (kg/m^2)	28.3 ± 6.4 (n = 75)
SBP (mmHg)	117.6 ± 19
DBP (mmHg)	69.2 ± 13.1
Heart rate (b.p.m.)	71.7 ± 13.7 (n = 75)
NYHA class III/IV	40/62 (65%)
Treatments	
Furosemide equivalent diuretic dose (mg)	284 ± 196
Beta-blocker	52 (68%)
Gliflozin	24 (32%)
Sacubitril/valsartan	14 (18%)
Ivabradine	1 (1%)
ACEI/sartan	32 (42%)
MRA	34 (45%)
Thiazides	4 (5%)
Resynchronization	3 (4%)
Transcatheter mitral repair	5 (7%)
ICD	9 (12%)
Medical history	
Chronic kidney disease	44 (58%)
eGFR (mL/mn/1.73 m^2)	37.1 ± 16.9
Stroke	10 (13%)
Diabetes	25 (33%)
Hypertension	34 (45%)
Coronary disease	68 (39%)
Liver disease	15 (9%)
AF	98 (56%)
HF characteristics	
LVEF (%)	42.7 ± 14.5 (n = 68)
LVEF (categories)	
<40%	29/68 (43%)
40–50%	15/68 (22%)
>50%	24/68 (35%)
RV failure	35 (46%)
Signs of right HF	69 (91%)
Signs of left HF	37 (49%)
IVC diameter (mm)	24.2 ± 6.1 (n = 37)
US B-lines	13.7 ± 15.2 (n = 21)
Ischaemic cardiopathy	30 (39%)
Dilated cardiopathy	21 (28%)
Restrictive	10 (13%)
Valvular	25 (33%)
Hypertrophic	9 (12%)

Note: Values are expressed as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association; ACEi, angiotensin-converting enzyme inhibitor; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; RV, right ventricular; HF, heart failure; IVC, inferior vena cava; US, ultrasound.

min/1.73 m^2 increase, P < 0.0001), ACEi treatment (beta = 0.302, P = 0.0005) and addition of thiazide during the diuretic session (beta = 0.238, P = 0.0001) as significantly associated with higher diuresis, whereas transcatheter mitral-valve repair (beta = −0.456, P = 0.001), and elevated age (beta = −0.081 for each 10-year increase, P = 0.044) were associated with significantly lower diuresis. Neither the dose of background loop diuretics nor the dose of diuretics administered during the IV session was associated with diuresis.

Table 2 Intervention, outcomes and safety (N = 175 sessions)

In-session parameters	
Furosemide equivalent dose intervention (mg)	238 ± 67
Mega dose >300 mg furosemide	116 (65%)
High dose 161–300 mg furosemide	26 (15%)
Standard dose 41–160 mg furosemide	27 (15%)
Low dose <41 mg furosemide	6 (3%)
Thiazides during treatment	74 (42%)
Session outcomes	
Diuresis (L)	1.0 ± 0.6 (n = 168)
Natriuresis (mmol/L)	92.6 ± 25.0 (n = 141)
Weight loss (g)	610 ± 636 (n = 145)
Hospitalizations	
Hospitalization immediately post-session	22 (13%)
Non-immediate hospitalization within 7 days post-session	10 (6%)
Hospitalization during 7 days post-session	32 (18%)
Laboratory variables	
Creatinine (mg/L)	
At baseline	19.3 ± 13.6 (n = 169)
At 48 h	19.2 ± 7.7 (n = 118)
At 1 week	19.5 ± 8.2 (n = 128)
WRF (absolute change in creatinine from baseline ≥ 3 mg/L)	
At 48 h	13/116 (11%)
At 1 week	19/126 (15%)
Hypokalaemia (<3.5 mmol/L)	
At baseline	12/173 (7%)
At 48 h	19/126 (15%)
At 1 week	10/122 (8%)

Note: Values are mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables.

Variables associated with natriuresis

In the final multivariable model for predicting natriuresis (*Table 3*), a high eGFR (P = 0.0005) and ACEi treatment (P = 0.018) were all significantly associated with higher natriuresis. Neither the dose of background loop diuretics nor the dose of diuretics administered during the IV session was associated with natriuresis.

Safety

The safety criteria at 48 h, 1 week as well as 1 month after diuretic therapy are summarized in *Table 3*. Hypokalaemia and worsening renal function (WRF) were infrequent.

Discussion

The main results of this study are that ambulatory 4-h IV loop diuretic sessions performed in the setting of a European tertiary care centre induced a diuresis of approximately 1000 mL

Table 3 Linear mixed model for predicting diuresis/natriuresis

	Diuresis, L (N = 168 sessions)		Natriuresis, mmol/L (N = 141 sessions)	
	Beta (SE)	*P*-value	Beta (SE)	*P*-value
Age (per 10-year increase)	−0.081 (0.040)	0.044	2.49 (2.02)	0.22
Male	0.086 (0.097)	0.38	−6.05 (5.52)	0.28
DBP (per 10 mmHg increase)	0.062 (0.019)	0.0005	2.48 (1.44)	0.089
ACEI/sartan	0.302 (0.085)	<0.0001	10.83 (4.53)	0.018
Transcatheter mitral repair	−0.456 (0.139)	0.001	−21.22 (7.99)	0.009
eGFR (per 10 mL/min/1.73 m^2 increase)	0.160 (0.024)	<0.0001	4.40 (1.23)	0.0005
Hypokalaemia (<3.5 mmol/L)	−0.195 (0.129)	0.13	−16.76 (5.15)	0.001
Sodium (per 10 mmol/L increase)	0.221 (0.098)	0.026	18.17 (4.60)	0.0001
Furosemide equivalent dose intervention (per 100 mg increase)	0.00 (0.015)	0.98	−0.81 (0.72)	0.27
Thiazides during treatment	0.238 (0.061)	0.0001	1.32 (3.66)	0.72
Marginal R^2 (CI 95%)	0.495 (0.38–0.599)		0.330 (0.212–0.449)	
Conditional R^2 (CI 95%)	0.759 (0.685–0.818)		0.721 (0.636–0.789)	

Abbreviation: SE, standard error.

with a substantial sodium content, without causing significant complications.

This is the first study to report an outpatient IV diuretics session performed in a day hospital in the setting of a European healthcare system. The study population mainly included elderly and chronic patients who are representative of current hospital practice. It also comprised patients with advanced heart failure and very high diuretic doses, which ensured a fair external validity in a variety of settings. In the specific setting stated above, in which repeated laboratory assessments are easily accessible, this outpatient management through day hospital sessions appeared safe.

We identified that background use of renin-angiotensin blockers and the addition of thiazide during the session sharply increased diuresis and natriuresis. Importantly, renin/angiotensin blockers have been shown to feature decongestion[3,5] properties, as they counteract sodium avidity related to neuro-hormonal activation. The increase in diuresis and natriuresis with thiazide use during IV diuretic sessions suggests that this strategy can be helpful in selected patients to optimize outpatient management. However, its use should be individualized, as studies such as CLOROTIC[10] have shown increased risks of acute kidney injury and hypokalaemia, highlighting the need for careful safety monitoring.

Lower eGFR, chronic use of thiazide, and a history of transcatheter mitral valve implantation were associated with lower diuresis and/or natriuresis. This is likely related to the very high-risk profile of these patients, in whom a high level of diuretic resistance may exist. In this particular population, using strategies to increase diuretic response may be wise. We acknowledge that no definitive conclusions can be drawn regarding transcatheter mitral valve implantation given the very small proportion of patients concerned (7%). In our cohort, TEER was performed as a rescue therapy in inoperable patients with severe mitral regurgitation, which mainly reflects the advanced stage of heart failure in this subgroup. Therefore, the observed association is likely related to the intrinsic severity of the underlying cardiac condition rather than the intervention itself.

The fact that neither the background dose of loop diuretics nor the dose of IV diuretics used during the session was associated with diuresis/natriuresis may indicate that the protocol used[4] is well calibrated. Indeed, the intrinsic level of diuretic need/resistance is seemingly offset by the dose of IV loop diuretics administered during the session, since it was not retained as significantly associated with diuresis/natriuresis. Although these high doses may not reflect those commonly used in routine outpatient practice, they were selected to provide an aggressive decongestive strategy over a short 4-h period. This design allows close monitoring during the session, supporting both the feasibility and safety of this approach. The absence of dose adjustment according to renal function could be viewed as a limitation, particularly given the established role of eGFR in predicting diuretic resistance.

In conclusion, we show herein that ambulatory 4-h IV loop diuretic sessions induce a diuresis of approximately 1000 mL containing a sizeable sodium content, without causing significant complications. Background use of renin-angiotensin blockers and the addition of thiazide during the session increase diuresis and natriuresis. The means to maximize the efficacy of these ambulatory IV diuretic sessions should be further explored in order to facilitate their use as an alternative to conventional hospitalization.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Diuretic protocol (from Buckey and al.).

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