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Short and long-term effects of continuous versus intermittent loop diuretics treatment in acute heart failure with renal dysfunction

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Abstract Intravenous loop diuretics are still the cornerstone of therapy in acute decompensated heart failure, however, the optimal dosage and administration strategies remain poorly defined particularly in patients with an associated renal dysfunction. This is a single-center, pilot, randomized trial involving patients with acute HF and renal dysfunction. Patients were assigned to receive continuous furosemide infusion (cIV) or bolus injections of furosemide (iIV). Primary end points were the evaluation of urine output volumes, renal function, and b-type natriuretic peptide (BNP) levels during treatment time. Secondary end point included: weight loss, length of hospitalization, differences in plasma electrolytes, need for additional treatment, and evaluation of cardiac events during follow-up period. 57 patients were included in the study. The cIV group showed an increase in urine output (2,505 ± 796 vs 2140 ± 468 ml/day, $p < 0.04$) and a more significant decrease of BNP levels in respect to the iIV group (679.6 ± 397 vs 949 ± 548 pg/ml, $p < 0.04$). We observed a significant increase in creatinine levels (1.78 ± 0.5 vs 1.41 ± 0.3 mg/dl, $p < 0.01$), and a reduction of the estimated glomerular filtration rate in cIV (44.8 ± 6.1 vs 46.7 ± 6.1 ml/min, $p < 0.05$). We observed a significant difference in eGFR ($p = 0.01$), creatinine ($p = 0.02$) and BNP levels ($p = 0.03$) from baseline to the end of treatment in both groups. A significant increase of in-hospital additional treatment as well as length of hospitalization was observed in cIV. Finally, cIV revealed a higher rate of adverse events during the follow-up period ($p < 0.03$). cIV appears to provide a more efficient diuresis and BNP level reduction during hospitalization, however, it was associated with increased rate of worsening renal function during hospitalization. cIV also appears related to a longer hospitalization and an increased number of adverse events during follow-up. For all of these reasons, a larger multi-center study is required to determine whether high-dose diuretics are responsible for worsening renal function and to define the best modality of administration.

Keywords Heart failure · Loop diuretics · Renal function · BNP

Abbreviations

AKI	Acute kidney injury
ADHF	Acute decompensated heart failure
BNP	B-type natriuretic peptide
CHD	Coronary heart disease
cIV	Continuous infusion
iIV	Intermittent infusion
eGFR	Estimated glomerular filtration rate
Hb	Hemoglobin
HF	Heart failure
Hct	Hematocrit
LVEF	Left ventricular ejection fraction
RBC	Red blood cells

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Introduction

The use of intravenous loop diuretics is still the cornerstone of acute decompensated heart failure (ADHF) treatment, especially in patients admitted with pulmonary congestion and volume overload. Significant concerns have been raised regarding the risks and the benefits of loop diuretics, especially involving the modality of administration and mean dosage and administration regimens [1, 2]. Current Guidelines recommend the use of loop diuretics to reduce left ventricular filling pressure and peripheral fluid retention, and to avoid pulmonary edema. Despite the high prevalence of their use, high quality data supporting diuretic safety and efficacy in this setting are lacking. In particular, specific reports comparing intermittent versus continuous administration in a step by step modality infusion have not yet been reported. Renal dysfunction is a clinical condition often associated with high doses of loop diuretics and poor outcome; however, patients with severe Renal Insufficiency have often been excluded from clinical trials [4, 5]. Although loop diuretics are the most commonly used drugs in HF treatment, their short- and long-term effects are relatively unknown. Therefore, it remains unclear if continuous infusion of loop diuretics is better than intermittent infusion in terms of diuresis efficacy, worsening of renal dysfunction and long-term prognosis. Most of the reported studies do not provide a dose escalation algorithm with a fixed dosage administration and the best diuretic dosage amount [6, 7]. For all these reasons, we thought that a dose layout is currently lacking, and it appears mandatory to achieve a scheme for modality administration and step by step increasing dosing. Recently, a multi-center trial on this topic (DOSE HF) evaluated how various doses and regimes of loop diuretics affect renal function, clinical status and early mortality. This study did not reveal a better outcome in either primary or secondary end points when comparing continuous infusion to a bolus regimen [8]. Given the conflicting data from literature, we aimed to evaluate the effects of a continuous infusion of furosemide compared to a bolus daily regimen at similar doses by assessing changes in urine output volumes, renal function and b-type natriuretic peptide (BNP) levels in patients with ADHF and mild renal dysfunction in a fixed dose protocol study based on diuresis response. Secondary end points were weight loss, length of hospitalization, need for additional therapy during infusion period, electrolyte imbalance and follow-up evaluation during a 6 months post discharge observational period.

Methods

Study protocol

This was a prospective, randomized, open label, single center pilot study, comparing continuous with intermittent infusion of furosemide in patients admitted with a diagnosis of ADHF into our tertiary-care medical center. Patients were enrolled consecutively from the Department of Internal Medicine, Cardiology Section Centre into a Para-Intensive Unit (Siena, Italy) from April 2011 to December 2012. We initially evaluated 94 patients; 22 were excluded because of normal renal function at baseline, 11 for receiving different dosages of intravenous furosemide, 4 for isolated diastolic HF (following the Consort diagram). The remaining 58 patients were randomized to receive continuous or intermittent intravenous furosemide administration. All the enrolled patients had continuous ECG and blood pressure monitoring combined with urine output measurement.

Patients were eligible if they were admitted with a primary diagnosis of ADHF, randomized within 12 h after hospital presentation, and with evidence of volume overload (pulmonary congestion) on a chest X-ray study and had BNP levels >100 pg/ml. Patients also displayed mild to moderate renal dysfunction with creatinine values up to 1.4 mg/dl. Some patients were supported with non invasive ventilation before randomization. Once the initial 12 h dose was determined, patients were randomized using a 1:1 ratio using a computer-generated scheme to receive the furosemide dose either divided into a twice-daily bolus injection or in a continuous infusion (mixed as a 1:1 ratio in 5 % dextrose in water) for a time period ranging from 72 to 120 h. The randomization was casual, and the physicians did not previously know the assigned arm. The dose escalation and subsequent titration of furosemide was guided by clinical response in terms of urine output volume and body weight reduction (Fig. 1). Before randomization, renal function parameters and BNP levels were measured in all patients. Subsequent titration of the furosemide dosage was at the discretion of the attending physician, but was guided by a dose-escalation algorithm based on the treatment response (weight loss and urine output volume), symptom improvement, changes in renal function, electrolyte balance, and chest radiography. The specific doses of furosemide and the use of additional agents to manage ADHF (dopamine, IV vasodilators, hypertonic saline infusion) were decided based upon blood pressure measurements, renal function evaluation and diuresis response. Supplementary treatment was left to the discretion of the treating physician. The duration of infusion was continued

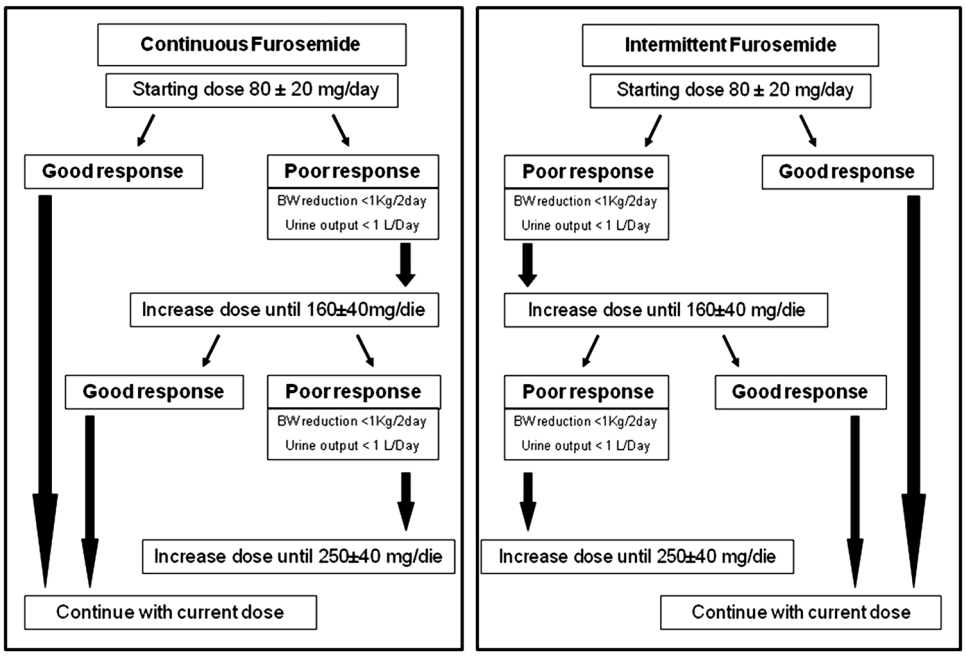

Fig. 1 Algorithm of diuretic treatment during randomization and study period

for up to 72 h, at 48 h the physicians had the possibility to adjust diuretic dose administration on the basis of the clinical response. After 72 h the treatment could be stopped or continued for an additional 36–48 h depending on the patient's condition and diuresis response. Acute kidney injury (AKI) was defined following the RIFLE criteria [9].

The frequency of laboratory determination of electrolytes, renal function and BNP after the infusion period until discharge was decided by the attending physician but was guided by a dose-escalation algorithm.

This trial was approved by the Local Investigational Human Review Board, and all patients gave their signed informed consent.

Inclusion criteria

Patients were included if they met the diagnostic criteria of acute HF associated with renal dysfunction. Patients enrolled had ADHF showing at least one of the following symptoms: dyspnoea, orthopnoea, peripheral oedema or major fatigue, In addition, patients had to exhibit at least two clinical signs such as rales, pulmonary congestion on chest radiography, jugular vein dilatation or a third cardiac heart sound. They also showed an impaired Left Ventricular Ejection Fraction (LVEF <45 %) with cardiac dilatation or pulmonary hypertension. Coronary heart disease information was gathered based on clinical history, evidence of Q waves on the electrocardiograms, and regional kinetic alterations on echocardiographic examination. In our study, renal dysfunction was defined as creatinine value >1.4 mg/dl and estimated glomerular filtration rate (eGFR) less than 50 ml/min·1.73 m^2.

Exclusion criteria

Patients were excluded if they had received more than two IV doses of furosemide or any continuous infusion of furosemide 1 month before the randomization, if they had end-stage renal disease or the need for renal replacement therapy (dialysis or ultrafiltration), isolated diastolic dysfunction or recent myocardial infarction. Patients with a systolic blood pressure lower than 80 mm Hg or with a serum creatinine level greater than 6.0 mg/dl were also excluded. Patients with recent contrast studies (cardiac catheterization, iodate liquid administration) were also excluded. Finally, patients taking neseritide thiazides or tolvaptan during the in-hospital period were excluded.

Outcome measurement

The 3 primary objectives were: (1) evaluation of renal function in terms of changes in creatinine levels and eGFR, (2) evaluation of mean urine output volume during the infusion period and (3) evaluation of BNP levels from admission to the end of treatment in the two groups. Secondary endpoints included: weight loss, electrolyte balance measurement, length of hospitalization, and need for additional treatment; follow-up evaluation of composite cardiac events in terms of death and re-hospitalization for cardiovascular causes.

Adverse events definition

We evaluated two different timing points of adverse events: in hospital and follow-up events. The in-hospital

events encompassed the need for: saline solutions treatment (for patients displaying Na^+ values <130 mEq during furosemide infusion) and dobutamine infusion (for patients with systolic blood pressure <90 mmHg), and major clinical adverse events in terms of sudden death, acute coronary syndrome, or acute renal insufficiency needing haemodialysis. The 6-months follow-up events encompassed: cardiac death, rehospitalization for all cardiovascular causes, and severe renal insufficiency needing hemodialysis.

Laboratory analysis

Complete blood counts with Hb, Hct, red blood cell count, serum creatinine, sodium, and potassium were performed at the time of admission to determine the baseline criteria, with subsequent testing performed each day during daily infusions, and again at the time of discharge. The eGFR was calculated using the modification of diet in renal disease [10].

Plasma BNP level was measured at the beginning and at discharge, using the quantitative immunofluorescence assay manufactured by Inverness (San Diego, CA, USA).The analytic sensitivity of the assay is <5 pg/ml, and the upper limit of normal is considered to be 400 pg/ml.

Statistical analysis

All data were analyzed with intention-to-treat. Continuous variables are expressed as mean ± standard deviation (SD) and compared with *t* test for independent groups. *p* values <0.05 were considered significant. The treatment groups defined by each treatment mode were compared with the use of univariate analyses to assess the independent relationship between the two methods of furosemide infusion and the respective outcomes. Kaplan–Meier methods were employed to generate survival plots that were compared using a log-rank test. Composite outcome were considered the sum of total adverse events in terms of mortality and rehospitalization for cardiac causes or acute renal insufficiency. All the analysis was performed by using the SPSS 13.0 for Windows (SPSS Inc, Chicago IL).

Sample size calculation

The sample size used was preliminarily calculated from each co-primary endpoint. We included the following assumptions: (1) a 30 % or more effect size in the difference between mean paired changes in continuous co-primary endpoints (eGFR, creatinine, BNP and diuresis); standard variation of each group data not exceeding 20 %; (2) alpha = 0.05 two-tailed and (3) power (1-beta) = 80 %. Thus, the considered sample size was 54 subjects (27 in each group), which was the larger among each endpoint; we assumed no patients would have withdrawn or been lost during follow-up.

Table 1 Clinical characteristics, risk factors and medication at admission of the enrolled sample

	cIV	iIV
Age	71 ± 7	73 ± 8
Gender		
Female	14	13
Male	16	15
Baseline weight	72	69.7
Blood pressure	120/75	125/80
Baseline creatinine (mg/dl)	1.63 ± 0.32	1.58 ± 0.24
eGFR (mg/ml)	45.2 ± 7.6	44.7 ± 7.7
Sodium baseline levels	137.2 ± 5	137.7 ± 5
Potassium baseline levels	4.19 ± 0.4	4.26 ± 0.5
Ejection fraction	34.3 ± 10	35.8 ± 8
NYHA class III	4	5
NYHA class IV	27	22
Risk factors (%)		
Diabetes mellitus	55.2	61.1
Hypertension	89.4	87.9
Dyslipidemia	72.4	75
Previous CAD	46.2	49.4
Atrial fibrillation (%)	36.6	41.3
Baseline BNP (pg/ml)	1,204 ± 693	1,099 ± 571
Medication at admission (%)		
Beta-blockers (%)	42	38
Aldosterone antagonists (%)	22	26
Ace inhibitors/angiotensin and or ARBs (%)	63	65
Nitrates (%)	55	58
Aspirin (%)	65	62
Anticoagulants (%)	22	25

eGFR estimated glomerular filtration rate, *BNP* B-type natriuretic peptide, *CAD* coronary artery disease, *cIV* continuous infusion, *iIV* intermittent infusion, *ARBs* angiotensin receptor blockers

Results

A total of 58 consecutive patients with acute HF and renal dysfunction were randomly assigned to one of the two groups. One patient was excluded from the analysis because of missing data regarding various laboratory measurements. No patients died during hospital stay, and all patients who needed dopamine infusion (n. 23) were able to be discharged routinely. The group that received the continuous infusion of furosemide (cIV), consisted of 30 patients. The second group that received the same drug in

Table 2 Differences in urine output volumes, renal function and BNP levels in both groups

	cIV	iIV	*p* value
Urine output/24 h (ml)	2,505 ± 796	2,140 ± 468	0.04
Creatinine AT (mg/dl)	1.78 ± 0.5	1.51 ± 0.3	0.01
eGFR AT (ml/min·1.73 m^2)	44.8 ± 6.1	46.7 ± 6.1	0.05
BNP AT (pg/ml)	679.6 ± 397	949 ± 548	0.04

eGFR estimated glomerular filtration rate, *BNP* B-type natriuretic peptide, *AT* after treatment, *cIV* continuous infusion, *iIV* intermittent infusion

Table 3 Difference in Δ laboratory parameters and clinical factors between each group from the admission to the discharge

	cIV	iIV	*p* value
Δ Creatinine AT (mg/dl)	−0.10 ± 0.30	−0.50 ± 0.34	0.02
Weight loss (kg)	−4.4 ± 2.1	−3.8 ± 3.1	0.39
Δ eGFR AT (ml/min·1.73 m^2)	−3.18 ± 2.45	−1.93 ± 2.90	0.01
Δ Sodium (mEq)	−2.3 ± 5.2	−3.5 ± 6.5	0.28
Δ Potassium (mEq)	−0.5 ± 1.1	−0.4 ± 0.7	0.83
Δ BNP AT (pg/ml)	−525 ± 615	−148 ± 463	0.03

eGFR estimated glomerular filtration rate, *BNP* B-type natriuretic peptide, *AT* after treatment, *cIV* continuous infusion, *iIV* intermittent infusion

bolus injections twice a day (iIV), consisted of 27 patients. The mean doses of furosemide were similar in both groups during the infusion period, and the median time from presentation to randomization was 16 h. Table 1 shows the patients' characteristics of each group at admission. The mean age was 72 ± 8 years, the mean ejection fraction was 35 ± 10 %, the mean creatinine level was 1.7 ± 0.4 mg/dl, and the mean BNP level was 1,156 ± 640 pg/ml. NIV therapy was performed in eight patients at hospital admission during the first 12 h, before enrollment. Among our patients, 64 % had ACE-inhibitors (enalapril or ramipril) or angiotensin-receptor blockers, 40 % had beta-blockers, 24 % aldosterone antagonist and the 56 % were treated with nitrates. The median duration of study-drug administration was 112 ± 24 h (110 ± 24 in cIV vs 120 ± 36 h in iIV). The mean dosage of furosemide was 188 ± 70 in cIV vs 170 ± 80 mg/day in iIV (NS). The total amount of furosemide infusion was 1,030 ± 340 mg in cIV and 980 ± 380 mg in iIV (NS).Other clinical characteristics and risk factors were similar in both groups.

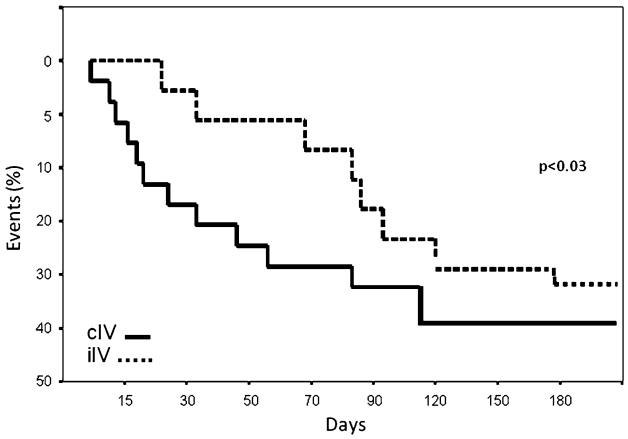

Fig. 2 Kaplan Meier curve for the combined risk of re-hospitalization and mortality at 180 days in two groups

Primary end points

The mean urine output volume/24 h was greater in cIV compared to the iIV arm (2,505 ± 796 vs 2,140 ± 468 ml, $p < 0.04$); analysis day by day during the infusion period revealed that most of the diuresis occurred during the second day after randomization (2,850 ± 720 cIV vs 2,560 ± 540 ml iIV, $p < 0.05$). Renal function analysis demonstrated a significant impairment in cIV in comparison with iIV after treatment: this was expressed by creatinine changes (1.78 ± 0.5 vs 1.41 ± 0.3 mg/dl, $p < 0.01$) as well as eGFR reduction (44.8 ± 6.1 vs 46.7 ± 6.1 ml/min/1.73 m^2, $p < 0.05$). Daily analysis of renal function demonstrated that AKI defined as creatinine >0.3 mg/dl, happened during the late infusion period (fifth day): percentage of AKI in cIV was 33 % vs 17 % in iIV group ($p < 0.01$). On the other hand, BNP levels were significantly reduced in the cIV group in comparison with the iIV group(679.6 ± 397 vs 949 ± 548 pg/ml, $p < 0.01$) (Table 2). Difference in eGFR ($p = 0.01$), creatinine ($p = 0.02$) and BNP levels ($p = 0.03$) from baseline to the end of treatment in each group were significant (Table 3).

Outcome analysis and secondary endpoints

In the CiV group there were eight patients rehospitalized, and six patients died during follow-up period. In the IiV group there were six patients rehospitalized, and three died. An increase in the number of adverse events was observed in the CiV group respect to iIV group in regards to re-hospitalization and for mortality (43 vs 34 %, $p < 0.03$). The Kaplan–Meier curve was significant for composite end points during the 180 days follow-up period (Fig. 2). Weight loss was measured after infusion period, and it was similar in both arms (−4.4 ± 2.1 in cIV vs −3.8 ± 3.1 kg in iIV; NS) (Table 3).

There were no significant differences in plasma electrolytes between both groups, although patients with cIV needed hypertonic saline solutions at a higher frequency (40 vs 19 %, $p < 0.01$). Dobutamine infusions

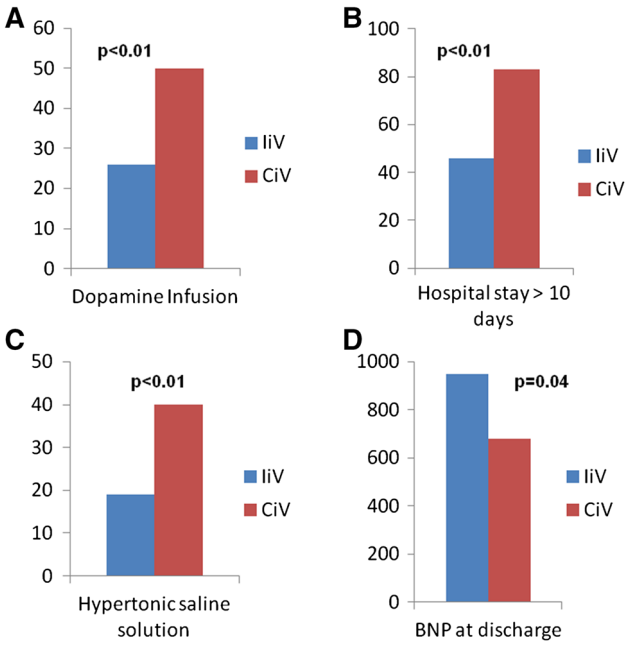

Fig. 3 **a** Difference in dopamine infusion between IiV (*blue columns*) and CiV (*red columns*) groups; **b** difference regarding hospitalization up than 10 gg between IiV (*blue columns*) and CiV (*red columns*); **c** difference in dopamine infusion between IiV (*blue columns*) and CiV (*red columns*) groups; and **d** difference in BNP values at discharge between IiV (*blue columns*) and CiV (*red columns*)

were administered more frequently in cIV in comparison with the iIV arm (50 vs 26 %, $p < 0.01$). The length of hospitalization was increased in cIV compared to iIV (14.3 ± 5 vs 11.5 ± 4.3, $p < 0.03$) (Fig. 3).

Univariate analysis of laboratory and clinical parameters from the follow-up period showed that admission creatinine >1.4 mg/dl (RR: 1.58 [1.15–2.04]; $p = 0.03$), admission eGFR <45 ml/min·1.73 m^2 (RR 1.69 [1.23–2.10]; $p = 0.01$) and BNP levels at discharge >500 pg/ml (RR: 2.06 [1.65–2.57]; $p = 0.01$) are all predictors of a poor outcome. On the other hand, neither BNP level at admission (RR: 0.94 [0.72–1.87]; $p = 0.18$) nor creatinine level at discharge (RR: 1.12 [0.77–1.53]; $p = 0.25$) and eGFR at discharge (RR: 0.81 [0.35–1.24]; $p = 0.14$) demonstrate any significant impact (Table 4).

Table 4 Univariate analysis of clinical predictors for adverse outcome including mortality and readmission for heart failure and other cardiac events or acute renal insufficiency

Parameters	Risk ratio	95 % CI of risk ratio	*p* value
Hospital stay (>10 days)	1.43	1.25–1.77	0.01
Creatinine (>1.4 mg/dl) at baseline	1.58	1.15–2.04	0.03
Creatinine (>1.5 mg/dl) at discharge	1.12	0.77– 1.53	0.25
eGFR (<45 ml/min·1.73/m^2) at baseline	1.69	1.23–2.10	0.01
eGFR (<45 ml/min·1.73/m^2) at discharge	0.81	0.35–1.24	0.14
BNP (>500 pg/ml) at discharge	2.06	1.65–2.57	0.01
BNP (>500 pg/ml) at admission	0.94	0.72–1.87	0.18
Hypersaline solution	1.13	0.84–1.46	0.08
Dobutamine infusion	1.49	1.06– 1.98	0.04
Continuous vs intermittent therapy	1.46	1.13–2.08	0.05

eGFR estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *IC* confidence interval

Discussion

The use of loop diuretics is essential in the management of HF, particularly during episodes of acute recurrent failure [3]. Although its use is approved by International Guidelines, currently there are no specific recommendations that show a clear benefit in HF outcome regarding both the administration modalities and the dosing [11]. Many authors believe that a dosage administration is merely a marker of disease severity, pointing to a higher degree of hemodynamic and kidney impairment [12, 13].

Our results demonstrate that despite a significant increase in the volume of the diuresis and a significant reduction of BNP levels in cIV group, there is a trend towards a higher rate of AKI during the hospitalization period in the same group when compared to the iIV arm. Moreover, the exact role of impaired renal function during hospitalization is currently under debate: some authors consider it as an important target and prognostic indicator, while others believe it is merely the final equivalent of systemic hemodynamic and neuroendocrine unbalance [14–16]. In our sample, worsening renal function during the hospitalization period seemed to have less clinical impact compared to the post discharge period.

Patients with cIV need more additional support therapy (saline solution and dobutamine) and a longer hospital stay. Although no differences in terms of adverse events were found between both groups during the hospitalization period, the post discharge period revealed a trend towards a worse prognosis in cIV (RR 1.46 [1.13–2.08], $p < 0.05$). These findings appear linked much more to basal renal dysfunction (RR 1.58 [1.15–2.04], $p < 0.03$) instead of impaired renal function at discharge as revealed by univariate analysis (Table 4). Nevertheless, we observed an apparent paradox consisting in BNP decrease associated with an impaired renal function in patients who were

submitted to a continuous treatment: some potential confounding contributors could be due to the worse hemodynamic and metabolic status linked to the modality of administration. Even if clinical and laboratory parameters are similar in the two groups, patients submitted to cIV may be exposed to more persistent kidney damage, which promotes neuroendocrine overdrive, leading to increased tubulo-glomerular feedback [2, 11]. In clinical practice, the use of loop diuretic is often empirical and established by physicians' experience instead of specific protocols and evidence. Besides, the impaired renal function during Acute HF hospitalization is a common phenomenon to which different authors assign different weight and importance: several studies indicate that worsening renal function is related to increased mortality and readmission, however, recent trials have questioned these findings. Nevertheless, it remains unclear whether WRF itself contributes to the poor outcome, or whether it is merely a marker of a more decompensated HF [14, 15, 18–20]. In patients with the Cardio-Renal syndrome treated with elevated doses of diuretics, compensatory pathophysiological mechanisms to maintain vascular resistance, such as non-osmotic stimulation of vasopressin secretion and activation of the renin angiotensin system (RAAS), have been observed [21]. Diuretic resistance is another factor often associated with WRF, and it may play a potential role in the occurrence of adverse effects. Therefore, hyponatremia is an associated clinical condition that could have a causal relationship that by itself leads to a diuretic resistance [22]. Although hyponatremia was not one of our primary endpoints, our findings evidenced that cIV infusion could impoverish Na^+ supplying with respect to iIV administration: the intermittent modality could avoid this event by salvaging Na^+ during a stop period.

The role of loop diuretics, their dosage, and the modality of administration, remain to be elucidated: recent analyses suggest that higher doses of diuretics are necessary in severe cases with more impaired renal function, thus adverse effects may result from disease severity [23]. In this context, Felker et al. [8] have recently published a multi-centre trial comparing loop diuretic dosages and administration modalities. Our findings provide evidence that both treatments are comparable on hard end-points during the early follow-up period, and they could not reveal a benefit of any one of the modality of treatments. Respect to the cited Trial, our study evaluated a longer follow-up period in patients with higher mean loop diuretic dosage. However, our results are in accordance with the DOSE trial: the Felker study does not reveal a different outcome despite worsening renal function in the cIV arm. These apparently contradictory data could be explained by several observations: the pathophysiological mechanism of the renal injury could be different in distinct reports and patients, moreover, blood pressure values and blood renal perfusion need to be included in the analysis. Therefore, additional therapy including exact fluid administration modality, and different diuretic protocol administration, are all confounding factors and potential biases [14, 20, 23]. Other studies in this field demonstrate conflicting results. Allen et al. [24] do not show any difference in hospital stay, urine output and creatinine levels between bolus and continuous infusion. On the other hand, Thomson et al. [25] show more favorable effects in the continuous arm, although a different diuretic dose administration was utilized in the different groups. These controversial findings could be due to the different etiology of renal dysfunction or different treatment protocols of administration. In this sense in our protocol we used a significant higher dosage respect to the previous published studies in which the mean dosage was 120 mg/die. All these concerns could partially explain some differences with respect to the literature. Perhaps our patients were sicker with more advanced congestion compared to previous studies.

Although our univariate analysis was executed in a small sample size, it demonstrated that BNP at discharge, baseline renal dysfunction and dobutamine infusion are the factors capable of predicting hospitalization and mortality rates during the follow-up period. From this point of view, our sample appears to have similar characteristics in comparison to the larger studies on ADHF [26, 27].

The BNP values trend deserves a more specific consideration: most trials demonstrate that a reduction of BNP is related to improved outcomes [28, 29]. Although we did not observe a more favorable outcome in group with cIV, analysis of all patients at discharge confirmed that a BNP cut off >500 pg/ml remains a potential predictor of higher adverse events rate. The current discrepancy could be due to the small number of patients studied, or to the difference in additional therapy between groups. Alternatively, we could hypothesize the prognostic impact of WRF should be more important with respect to BNP reduction. Taken altogether, these data suggest that loop diuretic efficacy is far from being universal. Further studies are required to determine whether high-dose diuretics are responsible for worsening renal function, and whether a higher rate of coexisting renal disease could be a marker of more severe heart failure.

Limitations

Although patients were randomly assigned to the treatment groups, this was not a blinded study. However, the mean dose administration and the clinical characteristics in both groups at randomization were similar. There are some

biases in the study protocol due to titration of furosemide dose according to the response, and non-uniform standard therapy (i.e., nitrate, ACE inhibitors, beta blockers) however, the mean dose of diuretic was similar in the two groups. Results could be partially influenced by the diuretic dose regime during the first 12 h before randomization. After the first 24 h of randomization, the titration of the furosemide dosage was guided based on the patient's response to the treatment. Most of the patients received open-label diuretic therapy during the period before randomization and admission to the hospital. For these reasons our findings cannot be extended to patients with newly diagnosed HF or to those with lower diuretic requirements. Our study did not explain the reasons for the decreased renal function during treatment, which could indicate a different pathophysiological disorder linked alternatively to a primitive renal disease, or secondary to infusion treatment or congestion. Concurrent evaluation of blood urea nitrogen could further clarify the primary defect. This is the next topic we would like to study in a larger sample. Infusion intake was not controlled since urine output and renal function could have been influenced. This was a single centre small non blinded study, it is prone to several forms of bias due to the nature of the protocol and intervention as well as to a lack of statistical power across any outcome. The multivariate analysis could be inadequate because of small sample size, and follow-up data should be taken with caution, for these reasons we intend to continue enrollment. Our study-sample was small, and was unsuccessful at detecting small but potentially significant differences in laboratory parameters, neither did it point to large differences in clinical outcomes. Therefore, our results may not be suitable for extension to other settings or populations.

Conclusions

In this preliminary, pilot study, cIV appears to provide a better BNP reduction and a more efficient diuresis in comparison to iIV, in patients with acute HF and renal dysfunction. However, continuous administration is associated with an increased rate of AKI after infusion treatment, longer hospital stay and the need for additional therapy. Moreover, cIV is related to impaired long-term outcome. For all of these reasons larger multi-centre studies appear mandatory to define the best approach and modality of administration.

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Conflict of interest None.

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