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Çağri Yayla[1,4] · Ahmet Akyel[2] · Uğur Canpolat[1] · Kadriye Gayretli Yayla[2] · Azmi Eyiol[3] · Mehmet Kadri Akboğa[1] · Sedat Türkoğlu[3] · Yusuf Tavil[3] · Bülent Boyaci[3] · Atiye Çengel[3]

[1] Department of Cardiology, Türkiye Yüksek Ihtisas Education and Research Hospital, Ankara, Turkey
[2] Department of Cardiology, Dişkapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey
[3] Department of Cardiology, Gazi University Faculty of Medicine, Ankara, Turkey
[4] Türkiye Yüksek Ihtisas Training and Research Hospital, Cardiology Clinic, Sihhiye/Ankara, Turkey

Comparison of three diuretic treatment strategies for patients with acute decompensated heart failure

Fluid removal by intravenous loop diuretics is an essential therapeutic option in acute decompensated heart failure (ADHF) to improve oxygenation and relieve symptoms associated with congestion [1]. Intravenous diuretic therapy is highly recommended in clinical practice guidelines and it should be initiated as soon as possible for improved prognosis and lower rehospitalization rates of patients with ADHF [2, 3]. Although rapid decongestion has been associated with reduced in-hospital cardiac death, it can cause impairment in renal function, resulting in increased hospital stay and poor prognosis [4–6]. Despite the known benefits and potential complications, the standard of care for loop diuretic regimens in ADHF patients is still unclear. In addition to controversies about dosage, there is also confusion about the optimal modality for administration. Previous studies showed that continuous infusion of high-dose loop diuretics offers more advantages than high-dose oral and intravenous bolus diuretic therapy [7, 8]. Several small-scale studies compared bolus injection (bI) with continuous infusion (cIV) alone or furosemide plus hypertonic saline solution (HSS), but none of them compared bI with both cIV and furosemide plus HSS in the same trial [9–12]. Therefore, we aimed to compare the efficacy and safety of these three diuretic regimens in patients with ADHF.

Methods

Study population

The present study was a single-centered, prospective, and randomized one. After approval from the institutional ethics committee, 43 patients hospitalized for ADHF with either reduced or preserved left ventricular ejection fraction (LVEF) were enrolled in the study between March 2011 and November 2012. All patients provided written informed consent. Patients who were admitted to the emergency department within the previous 24 h with a diagnosis of ADHF were included in the study if their pro-B-type natriuretic peptide (pro-BNP) level was greater than 300 pg/ml. Patients with any of the following criteria were excluded from the study: those with intravenous diuretic use before admission to hospital, serum creatinine levels greater than 2.0 mg/dl, and systolic blood pressure lower than 90 mmHg; patients requiring intravenous vasodilators or inotropic agents other than digoxin; and patients with suspected acute coronary syndromes.

The therapeutic regimens used in the study were prepared by an independent health care team before patient enrollment and each was defined as: Tx1 (cIV), Tx2 (bI), and Tx3 (furosemide plus HSS). In Tx1, an intravenous bolus infusion of 80 mg furosemide was given to 14 patients twice a day. In Tx2, a continuous furosemide infusion of 160 mg was given to 15 patients in 16 h per day. Tx3 group consisted of 14 patients and 160 mg furosemide and 150 ml of HSS containing 1.95 % NaCl and was given in 30 min. All of the treating physicians were blinded to the diuretic regimens. Patients were randomized to the therapeutic regimens by an initial computer algorithm blinded to the treating physicians.

The NaCl concentration of HSS varied between 1.4 and 7.5 % according to the serum sodium (Na) values in previous landmark studies [12–14]. Since all of the patients included in our study were normonatremic, we chose a concentration of 1.95 % NaCl for the HHS protocol in order to ensure standardization among patients. The study protocol was continued for 48 h. After this period, adjustment of the diuretic regimen was left to the treating physician's discretion on the basis of the patients' clinical response.

Demographic and clinical characteristics of the study population including age, gender, hypertension, diabetes mellitus, smoking, previous medications, and ischemic or nonischemic etiology of heart failure were recorded. Laboratory tests including complete blood count, blood urea nitrogen (BUN), serum creatinine, pro-BNP, serum uric acid, and electrolytes were undertaken for all participants. Renal function tests were repeated daily. Baseline weight on admission and daily weight measurements in the early

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Table 1 Baseline characteristics of the study groups

Variables	cIV ($n=15$)	bI ($n=14$)	HSS ($n=14$)	p
Demographic and clinical data				
Age, years	65.4 ± 12.2	71.7 ± 10.7	70.6 ± 8.2	0.24
Male gender, *n* (%)	8 (53.3)	7 (50.0)	9 (64.3)	0.72
Body weight, kg	85.4 ± 17.3	78.5 ± 18.1	79.0 ± 17.2	0.57
Diabetes mellitus, *n* (%)	5 (33.3)	7 (50)	9 (64.3)	0.24
Hypertension, *n* (%)	11 (73.3)	11 (78.6)	12 (85.7)	0.71
Ischemic etiology, *n* (%)	7 (46)	4 (28.6)	10 (71.4)	0.24
Atrial fibrillation, *n* (%)	5 (33.3)	7 (50)	4 (28.6)	0.29
LVEF, %	41.1 ± 15.7	44.8 ± 9.9	40.5 ± 16.9	0.72
Laboratory data				
Baseline BUN, mg/dl	24.1 ± 8.3	25.2 ± 16.5	22.1 ± 7.2	0.76
Baseline serum creatinine, mg/dl	1.10 ± 0.26	0.93 ± 0.32	0.96 ± 0.29	0.27
Serum Na, mEq/L	136.2 ± 5.2	137.8 ± 4.3	138.3 ± 5.0	0.49
NT-proBNP, pg/ml	4765 ± 2844	3973 ± 3080	3979 ± 2576	0.51
Hemoglobin, g/dl	12.3 ± 2.5	12.4 ± 1.3	12.1 ± 1.5	0.88
Medications				
ACE inhibitor or ARB, *n* (%)	7 (46.7)	9 (64.3)	10 (71.4)	0.37
Aldosterone antagonist, *n* (%)	5 (33.3)	4 (28.6)	2 (14.3)	0.47
β-Blocker, *n* (%)	9 (60)	4 (28.6)	11 (78.6)	0.02
Oral furosemide, *n* (%)	9 (60)	9 (64.3)	10 (71.4)	0.80

LVEF left ventricular ejection fraction, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *bI* bolus injection, *BUN* blood urea nitrogen, *cIV* continuous intravenous infusion, *HSS* hypertonic saline solution, *NT-proBNP* N-terminal pro-brain natriuretic peptide

morning before breakfast were performed throughout the study period.

Laboratory measurements

Blood samples were taken from the antecubital vein in the morning after 12 h of fasting. The types of blood cells were determined by an automated blood count device (Beckman Coulter AU 2700 Plus , Beckman Coulter Inc., Hialeah, Fla.) by the method of electrical impedance. The pro-BNP level was measured using Cobas h 232 (Roche, Switzerland) devices with an immunoassay method.

Transthoracic echocardiography

Echocardiographic examination was performed using a VIVID 7 Dimension Cardiovascular Ultrasound System (Vingmed-General Electric, Horten, Norway) with a 3.5-MHz transducer. Echocardiographic examination was performed with the patient in the left lateral decubitus position. Ejection fraction was calculated using the modified Simpson method.

Endpoints

Prespecified study endpoints included the following: changes in body weight as an indicator of fluid loss, changes in the serum creatinine level from baseline to 48 h and from baseline to compensated state, and length of hospital stay. Renal dysfunction was defined as an increase in serum creatinine of ≥ 0.3 mg/dl from baseline during a course of intravenous diuretic therapy. [13]

Statistical analysis

Analyses were performed with the Statistical Package for the Social Sciences (SPSS) software version 17.0 for Windows (SPSS Inc., Chicago, Ill.). The Kolmogorov–Smirnov test was used to investigate the normality of distribution of continuous variables, which were defined as mean ± standard deviation. A one-Way ANOVA test was used to show the differences between the groups in continuous numeric parameters with normal distribution. Tukey's test was used to identify means that were significantly different from each other. Differences between treatment groups for the categorical variables were analyzed using the chi-square test. The Kruskal–Wallis test was used for comparison of more than two groups without normal distribution. Statistical significance was defined as $p < 0.05$.

Results

The mean age of the study population was 69.2 ± 10.7 years and 56 % of the participants were male. The mean LVEF was 42.3 ± 14.7 %. Baseline demographic and clinical characteristics as well as the laboratory data of the study groups are shown in **Table 1**. Baseline serum creatinine (cIV group 1.10 ± 0.26 mg/dl vs. bI group 0.93 ± 0.32 mg/dl vs. HSS group 0.96 ± 0.29 mg/dl; $p = 0.27$) and pro-BNP levels (cIV group 4765 ± 2844 pg/ml vs. bI group 3973 ± 3080 pg/ml vs. HSS group 3979 ± 2576 pg/ml; $p = 0.51$) were similar. There was no significant difference between baseline serum Na values (cIV group 136.2 ± 5.2 mEq/l vs. bI group 137.8 ± 4.3 mEq/l vs. HSS group 138.3 ± 5.0 mEq/l; $p = 0.49$).

Medication use on admission including oral furosemide was similar between groups except β-blocker usage, which was significantly lower in the bI group (cIV group 60 % vs. bI group 28.6 % vs. HSS group 78.6%; $p = 0.02$).

All patients were followed up daily until they became compensated. The mean total dose of furosemide received over the course of 48 h of the study protocol was similar for each study group. After 48 h, the serum creatinine level was significantly lower in patients treated with the bI regimen. Post hoc analysis with Tukey's test showed that this difference was only significant between the cIV vs. bI groups (cIV vs. bI, $p = 0.03$; cIV vs. HSS, $p = 0.66$; bI vs. HSS, $p = 0.22$). However, there was no significant difference in renal function between any of the study groups (**Table 2**). Although the serum creatinine level was lower in the bI group, there was no significant difference between the study groups according to changes in serum creatinine level over the course of the study (cIV group 0.16 ± 0.21 mg/dl vs. bI group 0.04 ± 0.15 mg/dl vs. HSS group 0.20 ± 0.21 mg/dl; $p = 0.08$). There was also no significant difference between the three

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Ç. Yayla · A. Akyel · U. Canpolat · K.G. Yayla · A. Eyiol · M.K. Akboğa · S. Türkoğlu · Y. Tavil · B. Boyaci · A. Çengel

Comparison of three diuretic treatment strategies for patients with acute decompensated heart failure

Abstract

Background. There are few prospective data available for establishing a standard diuretic administration regimen for patients with acute decompensated heart failure (ADHF). We aimed to assess the safety and efficacy of three regimens of furosemide administration in patients with ADHF with regard to diuresis, renal functions, and in-hospital outcomes.
Methods. A total of 43 patients who presented with ADHF were randomized into three groups: (a) continuous infusion (cIV) of 160 mg furosemide for 16 h/day ($n=15$); (b) bolus injections (bI) of 80 mg furosemide twice a day ($n=14$); (c) and administration of 160 mg furosemide plus hypertonic saline solution (HSS) as an infusion for 30 min once a day ($n=14$). All regimens were continued for 48 h. Study endpoints were negative fluid balance assessed by loss of body weight, change in the serum creatinine (baseline to 48 h and baseline to compensated state), and length of hospitalization.
Results. There was no significant difference in the mean change in serum creatinine level at the end of 48 h between groups ($p=0.08$). There was also no significant difference among groups regarding loss of body weight ($p=0.66$). A significantly shorter hospitalization was observed in patients treated with HSS compared with the other groups (cIV group 6.6 ± 3.4 days vs. bI group 7.9 ± 4.1 days vs. HSS group 3.7 ± 1.3 days; $p<0.01$).
Conclusion. All three furosemide regimens have similar renal safety and efficacy measures. However, administration of furosemide plus HSS may be the preferred diuretic strategy because of its shorter hospital stay.

Keywords

Furosemide · Diuretic therapy · Acute heart failure syndrome · Renal safety profile · Hospitalization

Vergleich dreier Diuretikatherapieschemata bei Patienten mit akut dekompensierter Herzinsuffizienz

Zusammenfassung

Hintergrund. Es lagen bisher nur wenige prospektive Daten vor, um ein Standardschema für die Diuretikagabe bei akut dekompensierter Herzinsuffizienz (ADHF) zu etablieren. Ziel war es, die Sicherheit und Wirksamkeit dreier verschiedener Schemata der Furosemidgabe bei Patienten mit ADHF in Bezug auf Direse, Nierenfunktion und stationärem Behandlungsergebnis zu untersuchen.
Methoden. Es wurden 43 Patienten, die sich wegen ADHF vorstellten, 3 verschiedenen Gruppen randomisiert zugewiesen: kontinuierliche Infusion (cIV) von 160 mg Furosemid für 16 h/Tag ($n=15$); Bolusinjektionen (bI) von 80 mg Furosemid 2-mal täglich ($n=14$) und Gabe von 160 mg Furosemid plus hypertonische Kochsalzlösung (HSS) als Infusion für 30 min einmal täglich ($n=14$). Alle Schemata wurden 48 h lang fortgesetzt. Studienendpunkte waren ein negativer Flüssigkeitshaushalt, ermittelt durch Verlust von Körpergewicht, Änderung des Serumkreatinins (Ausgangswert bis Wert nach 48 h und Ausgangswert bis Wiedererreichen eines ausgeglichenen Werts) sowie Krankenhausverweildauer.
Ergebnisse. Es bestand kein signifikanter Unterschied zwischen den Gruppen hinsichtlich der mittleren Änderung des Serumkreatinins nach 48 h ($p=0{,}08$). Auch gab es keinen signifikanten Unterschied zwischen den Gruppen in Bezug auf das Körpergewicht ($p=0{,}66$). Eine signifikant kürzere Krankenhausverweildauer wurde bei Patienten festgestellt, die mit HSS behandelt wurden (cIV-Gruppe: 6,6 ± 3,4 Tage vs. bI-Gruppe: 7,9 ± 4,1 Tage vs. HSS-Gruppe: 3,7 ± 1,3 Tage; $p<0{,}01$).
Schlussfolgerung. Jedes der 3 Anwendungsschemata für Furosemid kann mit ähnlicher Sicherheit in Bezug auf die Nierenfunktion und ähnlicher Wirksamkeit benutzt werden. Jedoch stellt möglicherweise die Gabe von Furosemid plus HSS aufgrund der kürzeren Krankenhausverweildauer die bevorzugte Diuretikatherapie dar.

Schlüsselwörter

Furosemid · Diuretische Therapie · Akute Herzinsuffizienz · Renales Sicherheitsprofil · Hospitalisierung

groups according to mean change in serum creatinine level after the patients became compensated (cIV group 0.36 ± 0.42 mg/dl vs. bI group 0.10 ± 0.28 mg/dl vs. HSS group 0.30 ± 0.42 mg/dl; $p=0.18$; **Fig. 1**). No patient in any group required hemodialysis or ultrafiltration. Although patients in the HSS group had greater body weight loss, the difference was not statistically significant (cIV group 4.6 ± 5.2 kg vs. bI group 4.1 ± 2.7 kg vs. HSS group 5.7 ± 3.6 kg; $p=0.66$; **Fig. 2**). Importantly, the HSS group had a shorter hospital stay than the other groups: (cIV group 6.6 ± 3.4 days vs. bI group 7.9 ± 4.1 days vs. HSS group 3.7 ± 1.3 days; $p<0.01$; **Table 3**; **Fig. 3**).

Discussion

Although furosemide is an indispensable constituent of the therapy for ADHF, its administration mode and dosage in clinical practice varies significantly and there have been few prospective clinical trials investigating the effectiveness and safety of different furosemide regimens. In our prospective and randomized clinical study, we found no significant difference between continuous intravenous furosemide infusion, bolus furosemide injection, and intravenous furosemide plus HSS treatment regimens with respect to renal function assessed by serum creatinine levels and fluid removal measured by body weight loss. However, intravenous furosemide plus the HSS regimen resulted in a significantly shorter hospital stay. To the best of our knowledge, ours is the first trial comparing all three treatment regimens in one study.

Table 2 Renal function test results after treatment

	cIV	bI	HSS	*p*
BUN, mg/dl[a]	38.8 ± 15.3	34.1 ± 18.7	37.9 ± 16.8	0.72
Serum creatinine at 48 h, mg/dl[b]	1.27 ± 0.31	0.97 ± 0.27	1.17 ± 0.32	0.04
Serum creatinine, mg/dl[a]	1.46 ± 0.60	1.03 ± 0.40	1.27 ± 0.49	0.09
Serum Na, mEq/L[a]	134.0 ± 7.2	136.0 ± 3.8	136.7 ± 4.1	0.37

BUN blood urea nitrogen, *cIV* continuous intravenous infusion, *bI* bolus injection, *HSS* hypertonic saline solution
[a]Baseline to compensated state
[b]Tukey's test analysis showed that this difference was significant between the cIV and bI groups only

Table 3 Prespecified study endpoints

	cIV	bI	HSS	*p*
Length of hospitalization, days[a]	6.6 ± 3.4	7.9 ± 4.1	3.7 ± 1.3	< 0.01
Mean change in serum creatinine at 48 h, mg/dl	0.16 ± 0.21	0.04 ± 0.15	0.20 ± 0.21	0.08
Mean change in serum creatinine, mg/dl[a]	0.36 ± 0.42	0.10 ± 0.28	0.30 ± 0.42	0.18
Body weight loss, kg[a]	4.6 ± 5.2	4.1 ± 2.7	5.7 ± 3.6	0.66

cIV continuous intravenous infusion, *bI* bolus injection, *HSS* hypertonic saline solution
[a]Baseline to compensated state

Continuous intravenous infusion of furosemide has the advantage of consistent urine output ensuring a gradual reduction in intravascular volume, less neurohormonal activation, less vasoconstriction, and fewer side effects; however, its clinical superiority regarding efficacy has not yet been proven in human studies [9]. Aaser et al. [15] compared cIV with bI in ADHF and showed that there was no difference in urine output and changes in neurohormonal responses. Also, in a small study comprising 18 cardiac surgery patients, Copeland et al. [10] analyzed the efficacy of cIV and bI. Nine patients received 0.3 mg/kg of furosemide as a bolus injection with 6-h intervals and others received 0.05 mg/kg/h of furosemide as a constant infusion for 12 h. There was no significant difference between groups with respect to weight loss, creatinine clearance, changes in serum Na and potassium levels, and total urine volume for 12 h. The authors suggested that the lack of any difference between the groups was due to the study's short duration. In another study, Dormans et al. [16] compared cIV of high-dose furosemide with a single bI of same-dose furosemide in 20 patients with severe heart failure. They found that cIV of high-dose furosemide was more effective than bI of furosemide. A review of eight randomized studies comparing cIV with bI in 254 patients with heart failure showed that cIV was more efficacious and had fewer side effects than intermittent doses had [17]. Nevertheless, this result was entirely driven by a single study of 107 patients for whom the cIV arm consisted of 30-min twice daily furosemide plus infusion of HSS, which may have confounded the results [14]. Excluding the HSS trial, a meta-analysis of the other seven trials did not display significant differences in urine volume or changes in serum creatinine levels between cIV and bI [9, 16, 17]. Felker et al. [18] compared the safety and efficacy of diuretic strategies in 308 patients with ADHF. Patients were randomized to either a bolus of furosemide every 12 h, or cIV of furosemide at a dose equal to the patient's previous oral dose or a dose 2.5 times greater than the previous oral dose. There was no significant difference in serum creatinine among the groups. They emphasized that use of a continuous placebo infusion in patients treated with bI rendered their study different to previous ones. In this way, the patients remained in the supine position longer, which may have contributed to increasing diuresis. Allen et al. [9] compared twice-daily bI with cIV in 41 patients with HF. The mean dose of furosemide was similar between the two groups over the first 48 h. There was no significant difference between the bI and cIV groups from admission to the third day of hospitalization or hospital discharge. In a study that included 94 patients with refractory congestive heart failure, researchers compared the effects of 500–1,000 mg intravenous furosemide plus HSS twice a day in 30 min with a similar dose of furosemide alone for 4–6 days. There was a significant reduction in length of hospitalization and a significant increase in daily diuresis in the HSS group. [12] In another study, length of hospitalization was shortened and better BNP reduction was observed in the HSS regimen compared with bI furosemide alone [19].

After bI, the serum drug concentration diminishes quickly below threshold values. If diuretic therapy is not given at certain intervals, more Na is reabsorbed from the distal tubules and eventually Na retention that predisposes to diuretic resistance may occur. Intermittent bI treatment is a simple method to prevent diuretic resistance without limiting the mobility of the patient. cIV is associated with lower peak plasma concentrations, which can be linked to less frequent side effects. cIV causes a more stable diuretic exposure to the tubule, possibly decreases the rebound phenomenon, and preserves more consistent diuresis [20].

HSS augments the effect of furosemide by temporarily increasing serum Na concentration. Thus, there is a sustained and sufficient delivery of Na to the tubular lumen of Henle's loop concomitant with the period of the pharmacological effect of furosemide [21]. It is likely that HSS plays a role in lessening diuretic resistance [12]. Besides, HSS treatment stimulates release of vasodilator mediators such as prostacyclin and nitric oxide [22, 23]. Moreover, it was shown in many studies that HSS facilitates heart failure compensation with more effective diuresis and less deterioration in renal function [11, 12, 24, 25]. Administration of HSS with high doses of loop diuretics reduces neurohormonal stimulation as well as diuretic-related renal dysfunction [26]. However, administration of HSS without concomitant intravenous furosemide may have unfavorable effects. Increased concentrations of NaCl may be perceived by the macula densa and conversion of adenosine triphosphate to adenosine is increased with subsequent vasoconstriction owing to tubuloglomer-

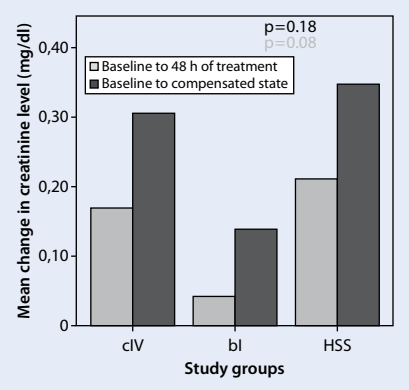

Fig. 1 ▲ Comparison of serum creatinine levels from baseline to 48 h and from baseline to compensated state between groups. *cIV* continuous intravenous infusion, *bI* bolus injection, *HSS* hypertonic saline solution

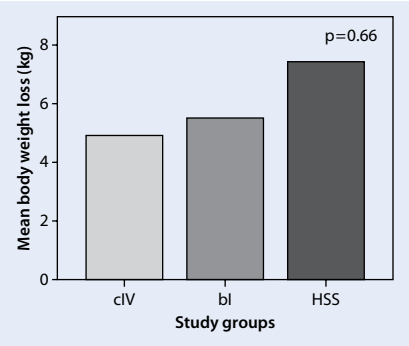

Fig. 2 ▲ Comparison of negative fluid balance assessed by loss of body weight between groups. *cIV* continuous intravenous infusion, *bI* bolus injection, *HSS* hypertonic saline solution

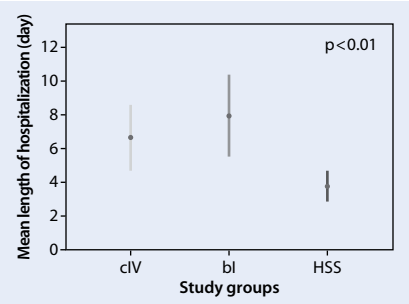

Fig. 3 ▲ Mean length of hospitalization was significantly lower in the HSS group compared with the cIV and bI groups. *cIV* continuous intravenous infusion, *bI* bolus injection, *HSS* hypertonic saline solution

ular feedback. However, concomitant administration of furosemide with HSS suppresses tubuloglomerular feedback, renal vascular resistance, and hypernatremia [27, 28].

The efficacy of various concentrations of HSS has been evaluated in patients with heart failure [26, 29, 30]. It was reported that infusion of 7.5 % NaCl solution resulted in vasodilatation and increased coronary and renal blood flow in experimental shock models [31, 32]. While comparing the efficacy of intravenous furosemide alone with intravenous furosemide plus HSS, Parrinello et al. [19] administered HSS concentrations according to the pre-randomization serum Na levels, ranging from 1.4–2.4 % for patients with serum Na values >135 mEq/l to 4.6 % for patients with serum Na values <125 mEq/l. As mentioned, since all of the patients included in our study were normonatremic, we preferred to use an HSS concentration of 1.95 %NaCl in order to ensure a standardized HSS treatment protocol.

Unlike previous studies, bI was not administered before treatment with cIV of furosemide in the present study. Thus, the superiority of cIV therapy could have been overshadowed by the lower furosemide concentrations achieved. In our trial, the change in renal function showed a nonsignificant trend toward improvement in the bI group. Small volumes of HSS plus loop diuretic can be a very effective and valuable method for reducing the potential detrimental effects of neurohormonal stimulation and deterioration of renal function [26]. HSS infusion causes a quick increase in extracellular NaCl concentration, which results in an increase in osmotic pressure, rapid fluid mobilization into the vascular compartment, and improved renal blood flow [24, 33, 34]. Previous studies showed that [35, 36] renal failure is not only a predictor of heart failure severity but it can also play a causative role in the progression of heart failure [37]. Several studies have shown the association between worsening renal function and poor outcomes [4, 35, 36]. Thus, a diuretic regimen should be able to quickly resolve congestion without impairing renal function. For this purpose, addition of plasma expanders such as HSS solution (2.4–3.5 % NaCl) or albumin (25 % albumin) to the diuretic therapy offers higher renal safety in heart failure patients with widespread edema and diuretic resistance even if they do not have hyponatremia or hypoalbuminemia [11]. In our study, there was a slight increase in creatinine levels in the HSS group. The shorter duration (48 h) and lower concentration of HSS (1.95 % NaCl) compared with other studies might have prevented the favorable effects of HSS on renal function. The HSS regimen can be preferred for diuretic treatment beyond 48 h, when favorable effects of this treatment modality can be seen on renal functions.

Paterna et al. showed a significant reduction in the length of hospital stay with HSS treatment in their study. However, there was not a significant difference in regard to weight loss between the furosemide plus HSS regimen and furosemide alone [29]. In the present study, the length of hospital stay was shorter but weight loss was only nonsignificantly higher in the HSS group compared with the other groups, possibly due to the relatively small study population.

Limitations

Our study has some limitations. First, it was a single-center study with a relatively small sample size of selected patients. Second, since the initial assessment and immediate management of heart failure patients was performed by the emergency medicine physicians, we could not find many patients without previous intravenous diuretic use and therefore could not include a higher number of eligible patients. In addition, the mean change in proBNP levels was not assessed at the end of the follow-up, because it has a slow clearance and meaningful changes during such a short time were not expected.

Conclusion

Furosemide plus HSS treatment resulted in a significant reduction in hospital stay compared with other diuretic regimens in the present study. However, all three furosemide regimens were found to have similar safety in patients with ADHF. The relatively small study population may have prevented the occurrence of positive effects of HSS on renal function. In addition, there could be many unknown factors that might play a role in the effectiveness of diuretic therapy. Thus, large-scale randomized and controlled studies

are required to confirm the results of the present study and to elucidate the exact role of HSS in heart failure treatment.

Corresponding address

Ç. Yayla MD
Türkiye Yüksek Ihtisas Training and Research Hospital, Cardiology Clinic
06100 Sihhiye/Ankara
cagriyayla@gmail.com

Compliance with ethical guidelines

Conflict of interest. Ç. Yayla, A. Akyel, U. Canpolat, K. Gayretli Yayla, A. Eyiol, M.K. Akboğa, S. Türkoğlu, Y. Tavil, B. Boyaci, and A. Çengel state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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