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Original Article

Continuous infusion of furosemide versus intermittent boluses in acute decompensated heart failure: Effect on thoracic fluid content

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ABSTRACT

Introduction: The administration of loop diuretics in the management of acute decompensated heart failure (ADHF) whether IV boluses or continuous infusion is still controversial. We intended to evaluate differences between the two administration routes on the thoracic fluid content (TFC) and the renal functions.

Methods: Sixty patients with ADHF admitted to the critical care medicine department (Cairo University, Egypt) were initially enrolled in the study. Twenty patients were excluded due to EF > 40%, myocardial infarction within 30 days, and baseline serum creatinine level > 4.0 mg/dL. Furosemide (120 mg/day) was given to the remaining 40 pts who continued the study after 1:1 randomization to either continuous infusion (group-I, 20 pts) or three equal intermittent daily doses (group-II, 20 pts). Subsequent dose titration was allowed after 24 h, but not earlier, according to patient's response. No other diuretic medications were allowed. All patients were daily evaluated for NYHA class, urine output, TFC, body weight, serum K^+, and renal chemistry.

Results: The median age (Q1–Q3) was 54.5 (43.8–63.8) years old with 24 (60%) males. Apart from TFC which was significantly higher in group-I, the admission demographic, clinical, laboratory and co-morbid conditions were similar in both groups. There was statistically insignificant tendency for increased urine output during the 1st and 2nd days in group-I compared to group-II (p = .08). The body weight was decreased during the 1st day by 2 (1.5–2.5) kg in group-I compared to 1.5 (1–2) kg in group-II, (p = .03). These changes became insignificant during the 2nd day (p = .4). The decrease of TFC was significantly higher in group-I than in group-II [10 (6.3–14.5) vs 7 (3.3–9.8) $k\Omega^{-1}$ during the first day and 8 (6–11) vs 6 (3.3–8.5) $k\Omega^{-1}$ during the second day in groups-I&II respectively, P = .02 for both]. There was similar NYHA class improvement in both groups (p = .7). The serum creatinine was increased by 0.2 (0.1–0.5) vs 0 (−0.1 to 0.2) mg% and the CrCl was decreased by 7.4 (4.5–12.3) vs 3.1 (0.2–8.8) ml/min in groups-I&II respectively (p = .009 and .02 respectively).

Conclusions: We concluded that continuous furosemide infusion in ADHF might cause greater weight loss and more decrease in TFC with no symptomatic improvement and possibly with more nephrotoxic effect.

1. Introduction

Heart failure is a global public health burden, associated with high morbidity, mortality and cost. It occurs in 1–2% of adults in developed countries; this prevalence increase to about 8.4% in population above 70 years old.[1,2]

Diuretics, especially loop diuretics are commonly used in heart failure patients to alleviate symptoms of congestion, to improve exercise capacity,[3] and to reduce mortality risk.[4] The use of diuretics has however, many drawbacks. Rapid intravascular volume depletion and direct venodilation caused by diuresis may cause hypotension.[5] The use of loop diuretics is associated with activation of the renin-angiotensin-aldosterone and sympathetic nervous systems.[6,7] Furthermore, renal hypoperfusion induced by hypotension and the neuro-humoral activation may precipitate cardio-renal syndrome.[8,9] Hypokalemia is another commonly encountered complication that accompanies loop diuretics' administration.[10,11]

Intravenous loop diuretics are routinely administered either as intravenous boluses or continuous infusions. The most appropriate method of administration is still controversial. The use of

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continuous infusion may theoretically be more beneficial. Early studies showed that intravenous boluses are associated with paradoxical increase in systemic vascular resistance, increased neurohumoral activation and decreased cardiac indices.[9,12] The use of continuous infusion of loop diuretics was seen to increase diuretic efficacy and reduce diuretic toxicity by using lower doses in post cardiac surgery patients with heart failure.[13] On the other hand, the DOSE trial revealed no significant difference between continuous infusion and boluses in terms of efficacy and change from baseline renal functions.[14]

Impedance cardiography (IC) is a non-invasive method for continuous hemodynamic monitoring which is safe, reproducible and can be used across the wide spectrum of heart failure patients.[15] One of the valuable hemodynamic parameters that are assessed by IC is the thoracic fluid content (TFC). It is inversely related to the chest wall impedance-i.e.; as the TFC increases, chest wall impedance decreases-. TFC correlates with intravascular and extravascular fluid compartments in the chest.[16]

We intended in this study to compare intravenous furosemide administration as a continuous infusion versus intermittent boluses in patients with acute decompensated heart failure (ADHF) in terms of reducing TFC, clinical improvement and safety.

2. Patients and methods

This is a prospective, randomized, pilot study comparing continuous versus intermittent administration of intravenous furosemide in patients with a diagnosis of ADHF with evidence of volume overload. We included patients admitted to the critical care department, Cairo University Hospitals, Egypt in the period from November 2014 to July 2015 with volume overload. Volume overload was defined as: at least one symptom (dyspnea at rest, orthopnea or peripheral edema) plus at least one clinical sign (rales of pulmonary congestion, jugular vein dilatation, or a third heart sound).

We excluded from the study patients with an age of 18 years or less, patients with heart failure with preserved EF (EF > 40%), patients with recent myocardial infarction within 30 days of admission, patients with serum creatinine levels > 4.0 mg/dL and those who required renal replacement therapy during their hospital stay.

After enrollment, all patients were subjected to detailed history and clinical examination, emphasizing on the cause of heart failure, NYHA class, vital signs and urine output.

Complete blood count, liver function tests, cardiac biomarkers, serum creatinine, serum sodium and potassium were performed on admission and repeated daily for the 1st 3 days after admission. Creatinine clearance (CrCl) was estimated using the Cockcroft – Galt equation.[17]

All patients were randomized in a 1:1 ratio into two groups. Group I patients received furosemide infusion at a dose of 5 mg/h and Group II patients received furosemide at a dose of 40 mg every 8 h. Subsequent dose titration of furosemide was allowed only after 24 h of enrollment based on the patient's response.

The use of additional agents to manage ADHF (ACE-I/ARBs, Digoxin, Nitrates, Nor-adrenaline and/or Dobutamine) were decided based upon current guidelines of management of ADHF but no other types of diuretic agents were allowed during the study period.

Thoracic fluid content was measured using non-invasive electrical cardiometry device (ICON Cardiotronics, Inc, La Jolla, CA 92,307, Osypka Medical GmbH, Berlin, Germany). The device emits electrical current with high frequency-low constant amplitude that is interpreted by the device. This current is very low and is not harmful to patients. The measurement unit is $k\Omega^{-1}$. Normal value range is 25–35 $k\Omega^{-1}$.[18]

Electrical cardiometry was performed by applying 4 electrodes; 2 electrodes were applied to the neck on the left side (the 1st electrode placed above the root of the neck by about 5 cm and the 2nd electrode placed at the root of neck). The other 2 electrodes were applied to chest wall (one was placed on the level of xiphoid on the left side and the other placed 5 cm lateral to the previously placed electrode at level of anterior axillary line). Patient data including gender, weight, height and age were fed to the device before obtaining measurements. TFC was measured on admission and then 24 h and 48 h later. The decrease in TFC over time was estimated as Δ TFC. Δ TFC_1 represents the decrease during first 24 h (Δ TFC_1 = TFC on admission – TFC after 24 h) and Δ TFC_2 represents the decrease during the second day of admission (ΔTFC_2 = TFC after 24 h – TFC after 48 h).

All patients were monitored for hourly urine output for every kg of body weight (mL/kg/h) and weight reduction (weight reduction during 1st 24 h = body weight on admission – body weight after 24 h) (kg/day). The evaluated adverse effects included serum electrolytes, renal functions and occurrence of acute kidney injury (defined as acute elevation of serum creatinine $\geq$0.3 mg/dl within 48 h).[19] Occurrence of hypokalemia (defined as serum K^+ level $\leq$ 3. 5 meq/L) and the need of vasoactive and/or inotropic support were evaluated.

Other outcome parameters evaluated included average ICU length of stay (ICU-LOS) and in-hospital mortality.

Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review board at Cairo University.

2.2. Statistical methods

Data were prospectively collected and coded prior to analysis using the statistical package of social science (SPSS version 16). Normal distribution of different dependent variables in relation to their independent variables was studied. A variable was considered normally distributed if the Shapiro-Wilk's test had a P > .05.[20,21] and with z-value of skewness and kurtosis between −1.96 and +1.96.[22] Most of our variables were non-normally distributed and accordingly all continuous variables were expressed as median (25th percentile-75th percentile). Categorical variables were expressed as frequency and proportion.

Nonparametric Mann-Whitney U test was used for comparison between two groups as regard quantitative variable and Wilcoxon test was used for paired comparisons for TFC on admission and after 24 h. Chi-Square Test (x^2) was used for comparison between two groups about qualitative data. Exact test was used instead when the expected frequency is less than 5. P value $\leq$ 0.05 was considered statistically significant.

3. Results

A total of 60 patients were initially enrolled in the study. 11 patients were excluded for preserved ejection fraction (>40%), 4 for serum Creatinine > 4 mg/dL, and 5 for recent myocardial infarction within 30 days of admission. Thus, 40 patients (24 males and 16 females) with a median age (Q1–Q3) of 54.5 (43.8–63.8) years old were randomly assigned to one of the two groups; Group I (n = 20 patients) representing those who received furosemide in the form of continuous IV infusion and Group II (n = 20 patients) representing those who received furosemide in three daily intermittent boluses. The baseline demographic and clinical criteria of the patients' population are presented in Table 1.

Table 1
Baseline characteristics of the study population.

		Group I	Group II	P value
Age [median (Q1–Q3) years old]		53.5 (43.5–62.8)	57 (46–65)	.9
Male gender [No (%)]		13 (65%)	11 (55%)	.75
Body weight (kg)		87 (76.4–97)	78 (73–86)	.06
Co-morbidities [No (%)]	Smoking	6 (30%)	8 (40%)	.52
	Diabetes mellitus	10 (50%)	10 (50%)	1.0
	Hypertension	15 (75%)	12 (60%)	.5
	Dyslipidemia	10 (55%)	9 (45%)	.56
Etiology of heart failure [No (%)]	Ischemic	14 (70%)	14 (70%)	.58
	Idiopathic	6 (30%)	5 (25%)	
	Valvular	0	1 (5%)	
NYHA class on admission	III	5 (25%)	8 (40%)	.5
	IV	15 (75%)	12 (60%)	
Admission blood pressure [mean ± SD (mmHg)]	SBP	110 (106.3–117.5)	110 (110–120)	.7
	MAP	83.3 (78.3–86.7)	83.3 (76.8–86.7)	.1
	DBP	70 (70–77.5)	70 (60–70)	.4
Admission HR [mean ± SD (bpm)]		102 (95–110)	108 (91–115)	0.6
AF on admission [No (%)]		6 (30%)	7 (35%)	0.74
Echocardiographic findings	EDD (cm)	5.9 (5.2–6.4)	5.5 (5.3–6.5)	.7
	ESD (cm)	4.7 (4–5.2)	4.1 (3.4–6.2)	.3
	EF (%)	38 (27.3–41.8)	37 (30–40)	.8
Serum Na^+ [mean ± SD (meq/L)]		134 (130–136)	136 (132–138)	.2
Serum K^+ [mean ± SD (meq/L)]		4 (3.7–4.2)	3.9 (3.7–4.2)	.8
Admission serum creatinine [mean ± SD (mg/dL)]		1.9 (1.4–2.5)	1.7 (1.1–2.2)	.2
Admission serum BUN [mean ± SD (mg %)]		31.5 (20–47)	30 (20–30)	.9
Admission CrCl [mean ± SD (ml/min)]		47.1 (39–64.5)	61.7 (37.9–78.6)	.4
TFC on admission [mean ± SD ($k\Omega^{-1}$)]		64.5 (56–70.8)	57.5 (50.3–62.5)	**.03**

HR: Heart rate, AF: Atrial fibrillation, EDD: End diastolic dimension, ESD: End systolic dimension, EF: ejection fraction, Na^+: Sodium, K^+: Potassium, BUN: Blood Urea Nitrogen, CrCl: Creatinine Clearance, TFC: Thoracic Fluid Content.

The use of other medications in the management of heart failure was similar between both groups. Angiotensin converting enzyme inhibitors and beta blocking agents were used by 8 (40%) and 6 patients (30%) respectively in group I compared to 11 (55%) and 5 (25%) in group II (P = .53 and 1) while aldosterone receptors blockers and Digoxin were used by 9 (45%) and 8 patients (40%) compared to 15 (75%) and 7 patients (35%) in groups I and II respectively (P = .1 and 1).

3.1. Efficacy endpoints

Urine output during the first, second and third 24 h after admission was not found to be significantly different between the two groups. During the first day, median urine output was 1.6 (1.1–1.8) ml/kg/h in group I with furosemide infusion compared to 1.2 (1.1–1.5) ml/kg/h in group II with boluses therapy (P = .08). Urine output was 1.6 (1.3–1.8) and 1.6 (1.2–1.9) ml/kg/h in group I compared to 1.3 (1.1–1.6) and 1.4 (1.1–1.6) ml/kg/h in group II during the second and third days respectively (P = .08 and .1).

Body weight was significantly reduced during the first 24 h after admission in group I compared to group II [2 (1.5–2.5) kg vs 1.5 (1–2) kg, P = .03]. During second day of admission, the body weight was reduced by 2 (1.1–2.5) kg in group I compared to 2 (1.5–2) kg in group II (P = .4) (Fig. 1).

The median (Q1–Q3) values of TFC on admission were high for all patients 60.5 (54.3–69.3) $k\Omega^{-1}$ compared to normal range of 25–35 $k\Omega^{-1}$ [20] reflecting pulmonary congestion. In both groups, the TFC was significantly reduced after 24 h of furosemide therapy compared to baseline. It decreased from 64.5 (56–70.8) $k\Omega^{-1}$ to 52.5 (47.5–57.8) $k\Omega^{-1}$ in group I (P = <0.001) and from 57.5 (50.3–62.5) $k\Omega^{-1}$ to 50.5 (41–60.8) $k\Omega^{-1}$ in group II (P = .001). The admission TFC values were significantly higher in group I compared to group II (P = .03) (Table 1).

The Δ TFC_1 was significantly higher in group I compared to group II [10 (6.3–14.5) $k\Omega^{-1}$ vs 7(3.3–9.8) $k\Omega^{-1}$, P = .02]. The Δ TFC_2 was 8 (6–11) $k\Omega^{-1}$ vs 6 (3.3–8.5) $k\Omega^{-1}$ in groups I and II respectively which was also significantly higher, P = .02 (Fig. 2).

The improvement of the NYHA class was not different between the two groups. The NYHA class was unimproved during the 1st 24 h in 5 patients from group I and 6 patients in group II and improved by 1 degree (e.g. from NYHA 4 to 3 or from NYHA 3 to 2) in 15 and 14 patients from groups I and II respectively (P = .7). Similar results were shown during the 2nd day of therapy without improvement of NYHA in 5 and 6 patients and improvement by 1 degree in 15 and 14 patients from groups I and II respectively (P = .6).

3.2. Safety endpoints

There was no statistically significant difference between the 2 groups regarding baseline serum creatinine level. However, the follow up serum creatinine level revealed a significant elevation after 48 h in continuous infusion group from the baseline. It was increased by 0.2 (0.1–0.5) mg % in group I compared to 0 (−0.1 to 0.2) mg % in group II, P = .009. The decline in CrCl was also significantly greater in group I compared to group II. It declined by 7.4 (4.5–12.3) ml/min and 3.1 (0.2–8.8) ml/min in groups I and II respectively, P = .02. The development of AKI was however, not significantly different in both groups occurring in 9 patients of group I (45%) compared to 5 patients of group II (25%), P = .3.

The hemodynamic consequence of the administration method was evaluated by the incidence of inotropic and/or vasopressor support need, which was not statistically significant between the two groups. Six of group I patients (30%) needed inotropic and/or vasopressor support compared to 3 (15%) of group II patients, P = .5.

The use of the furosemide infusion during the 1st 24 h was associated with a decrease in serum K^+ level by 0.1 (0.1–0.5) mEq/L and in serum Na^+ by 0 (−1 to 1) mEq/L while the bolus administration was associated with decreased serum K^+ by 0.1 (−0.3 to 0.3) mEq/L and increase serum Na^+ by 1 (−2 to 1) mEq/L. However, these differences were not statistically significant (P = .2 and 0.5 for serum K^+ and Na^+ respectively).

Hypokalemia was observed in 4 patients compared to 3 patients after 24 h of furosemide infusion and boluses respectively which

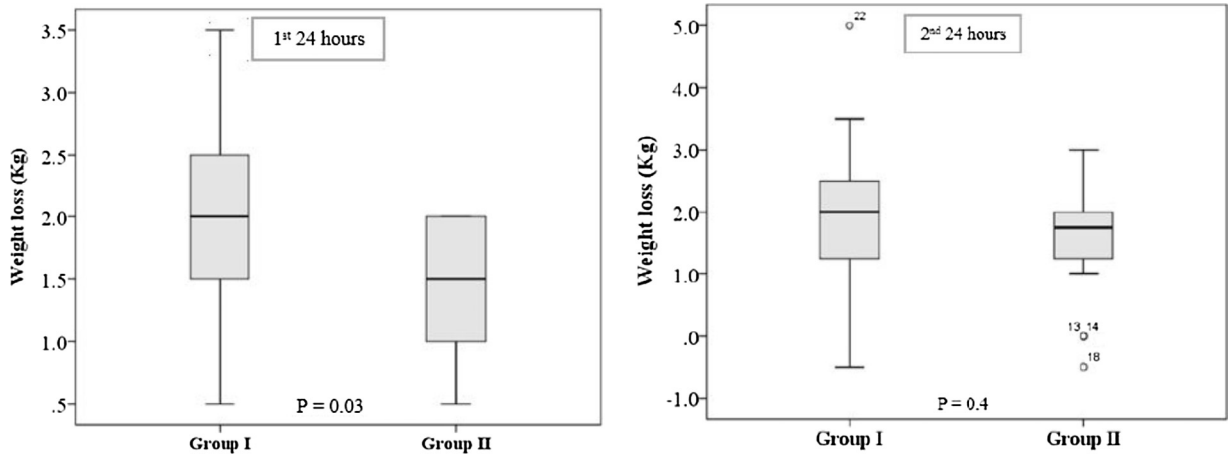

Fig. 1. Weight reduction during the hospital course.

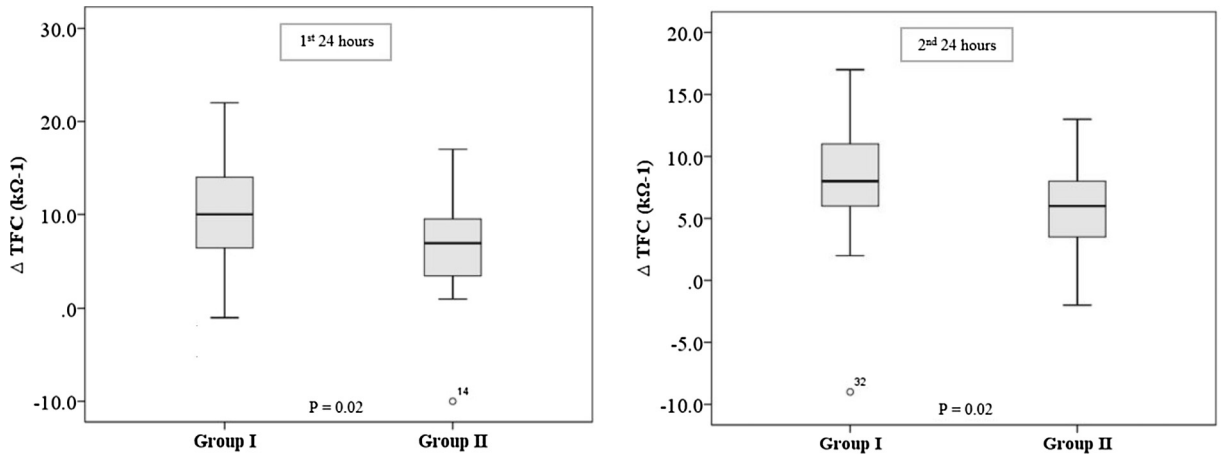

Fig. 2. Reduction of the TFC during the hospital course.

was found to be statistically insignificant (P = 1). However, after 48 h of therapy, it was found that hypokalemia significantly occurred more frequently in the continuous furosemide infusion patients (8 patients in group I developed hypokalemia after 48 h vs 1 patient in group II, P = .02).

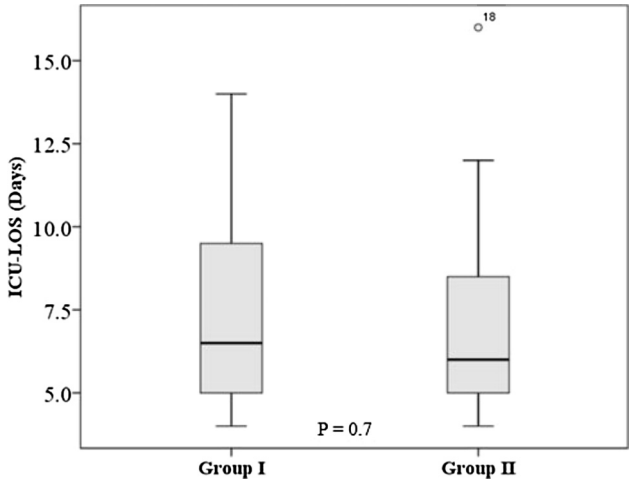

Fig. 3. The average ICU length of stay in both groups.

3.3. Outcome

We evaluated the effect of the furosemide administration method on the average ICU-LOS. There was no statistically significant difference in the average ICU-LOS between the two groups. It was 6.5 (5–9.8) days in group I compared to 6 (5–8) days in group II (P = .7) (Fig. 3). Only two patients died from each group during the hospital stay with 10% in-hospital mortality rate. Due to these small numbers, no further statistical inference was concluded for the association between the route of furosemide administration and the in-hospital mortality.

4. Discussion

Recent guidelines recommend the use of loop diuretics to improve pulmonary congestion, decrease the left ventricular pressures and reduce peripheral fluid retention.[23] However, the best method of administration is still not known. Many studies revealed contradictory results about the optimum administration. Some studies revealed beneficial results with continuous infusion[24–26] while others did not.[14,27] Many of these studies had only subjective efficacy endpoints as symptomatic improvement[14] and others had more objective endpoints as B type natriuretic peptide (BNP).[28] To our knowledge, there were no studies that compared different administration methods on the lung water objectively either

invasively through pulmonary artery catheter (PAC) or non-invasively by IC.

We evaluated the difference between intravenous infusion of furosemide in patients admitted with ADHF and intermittent boluses in terms of efficacy and safety. The efficacy was primarily evaluated by the TFC evaluated by ICON.

Transthoracic impedance cardiography was validated for the diagnosis and evaluation of treatment responsiveness in heart failure.[29,30] The TFC is one of the hemodynamic parameters which is measured by IC that reflects interstitial, intra-vascular and intra-alveolar fluid within the thorax. It was used effectively in ADHF patients[29–31] and was found to be comparable to the PAC for the evaluation of cardiac output[32,33] and pulmonary capillary wedge pressure.[34] It was also seen to be correlated with serum BNP levels in heart failure patients.[35]

We randomized 40 patients (24 males, 16 females) admitted with a primary diagnosis of ADHF by 1:1 randomization to 2 groups with equal doses of furosemide during the first 24 h administered as continuous infusion or intermittent boluses. There was no statistically significant difference between study groups regarding demographic data, co-morbidities, etiology of heart failure, and other clinical and laboratory findings.

In our study, TFC decreased significantly during the first two days in patients kept on furosemide infusion. This was not reflected on clinical benefits in terms of improved NYHA functional class. Body weight reduction was more obvious in continuous infusion during the first 24 h, but this difference was not significant during the second 24 h (after allowing dose adjustment).

Other earlier studies showed also that the continuous infusion is associated with greater diuresis.[26,36,37] In a Cochrane systemic review, it was shown that the continuous infusion had more diuretic effect and better safety profile. However, no clear recommendations were applied due to the poor quality of their available data that they considered.[25] In another study, continuous infusion caused more urine output and more reduction in plasma BNP.[28] Similar to our results, Llorens et al. showed that the use of continuous infusion caused more diuretic effect but with no symptomatic relief.[27]

The DOSE trial[14] was one of the largest prospective randomized trials that enrolled 308 patients evaluating the administration method of furosemide. They found no significant difference in the subjective patients' global assessment of symptoms. They found also no difference between the two methods regarding treatment failure. The net fluid loss and change in body weight were also similar in both groups. The DOSE investigators allowed a 50% increase in furosemide dose after 48 h in poor responders. The lack of efficacy of infusion method could be attributed to the higher need for increasing the dose and the higher total dose of furosemide they reported in the boluses group.[14] The lack of preferential diuretic effect of infusion in the DOSE trial could be also attributed to the absence of loading doses which efficacy was concluded by some other investigators.[38]

Like other studies,[39] our study showed no association between the diuretic effect and symptomatic relief in heart failure. This was explained by Dikshit et al.[5] who speculated that the symptomatic improvement of furosemide in ADHF is not only related to diuresis but also to venodilation.[5]

Concerning the safety outcomes, we elucidated a significant worsening in kidney functions (serum creatinine and CrCl), with a higher incidence of hypokalemia in infusion group compared to boluses group. Similar to these results, Palazzuoli et al. showed that continuous infusion resulted in higher serum creatinine and lower eGFR and lower serum potassium level with no significant difference in serum sodium.[28] They explained this deterioration in kidney functions by intravascular volume depletion caused by the more potent diuretic effect. Large volume diuresis causes early intravascular volume depletion before this is corrected by plasma refill of fluid from the extravascular space.[40] However, this was not consistent in other studies.[26,36,37] The DOSE trial showed similar change of serum creatinine level from baseline to 72 h between the two administration methods.[14]

The incidence of hypotension with the need of inotropic and/or vasopressor support showed statistically non-significant difference between both groups that agreed the results of the DOSE trial. On the contrary, other studies showed that the intermittent infusion caused more variations in urine output and blood pressure and recommended continuous infusion in hemodynamically unstable patients due to the more predictable urine output.[41]

There was no statistically significant difference in the average ICU-LOS between the two groups. These results were similar to that shown in the DOSE trial where there was no difference in the length of stay and in-hospital mortality between the two administration methods.[14] Another study showed however, an increased length of hospital stays and mortality with the use of continuous infusion of furosemide.[28] In these studies, the length of stay was a secondary outcome.

Our study was limited by the small sample size including only 20 patients in each group. The change of the dose of furosemide that was allowed after the 1st 24 h was not controlled and was left to the discretion of the treating physician. The comparison between the two administration modalities was accordingly possible only during the 1st 24 h. The baseline TFC was significantly higher in infusion group and accordingly, we compared the temporal change of TFC rather than their actual measures. We did not give loading doses of diuretics in the continuous infusion group. Copeland et al. found that the continuous infusion would result in a gradual increase of plasma levels and peaks after several hours of infusion.[38] The use of continuous infusion of furosemide needs to be evaluated especially in patients with chronic renal impairment and those with diuretic resistance.

5. Conclusions

In conclusions, despite that the use of continuous infusion of furosemide in ADHF might cause more diuresis and greater decease in TFC, this may be on the expense of a higher risk of deterioration in renal functions and may not translate into symptomatic improvement or decrease in ICU stay.

Conflict of interest

The authors declare that there are no conflicts of interest.

References

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93:1137–1146. https://doi.org/10.1136/hrt.2003.025270.
2. Redfield MM, Jacobsen SJ, Burnett Jr JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.
3. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol*. 2002;82:149–158.
4. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev 2012:CD003838. http://doi.org/10.1002/14651858.CD003838.pub3.
5. Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJ. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N Engl J Med*. 1973;288:1087–1090. https://doi.org/10.1056/NEJM197305242882102.
6. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Hear J*. 1987;57:17–22.

7. Knight RK, Miall PA, Hawkins LA, Dacombe J, Edwards CR, Hamer J. Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease. *Br Hear J*. 1979;42:316–325.
8. Sarraf M, Masoumi A, Schrier RW. Cardiorenal syndrome in acute decompensated heart failure. *Clin J Am Soc Nephrol*. 2009;4:2013–2026. https://doi.org/10.2215/CJN.03150509.
9. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, et al.. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 1990;82:1724–1729.
10. Greenberg Arthur. Diuretic complications. *Am J Med Sci*. 2000;319:10–24. https://doi.org/10.1016/S0002-9629(15)40676-7.
11. Hropot M, Fowler N, Karlmark B, Giebisch G. Tubular action of diuretics: distal effects on electrolyte transport and acidification. *Kidney Int*. 1985;28:477–489.
12. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med*. 1985;103:1–6.
13. Gulbis BE, Spencer AP. Efficacy and safety of a furosemide continuous infusion following cardiac surgery. *Ann Pharmacother*. 2006;40:1797–1803. https://doi.org/10.1345/aph.1G693.
14. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al.. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797–805. https://doi.org/10.1056/NEJMoa1005419.
15. Yancy Clyde, Abraham William T. Noninvasive Hemodynamic Monitoring in Heart Failure: Utilization of Impedance Cardiography. Congest Hear Fail 2003;9:241–50. http://doi.org/10.1111/j.1751-7133.2003.tb00021.x.
16. van de Water JM, Mount BE, Chandra KM, Mitchell BP, Woodruff TA, Dalton ML. TFC (thoracic fluid content): a new parameter for assessment of changes in chest fluid volume. *Am Surg*. 2005;71:81–86.
17. Pierrat A, Gravier E, Saunders C, Caira MV, Ait-Djafer Z, Legras B, et al.. Predicting GFR in children and adults: a comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas. *Kidney Int*. 2003;64:1425–1436. https://doi.org/10.1046/j.1523-1755.2003.00208.x.
18. Sadauskas Saulius, Naudžiūnas Albinas, Unikauskas Alvydas, Mašanauskienė Giedrė, Bakšytė Giedrė, Macas Andrius. Applicability of impedance cardiography during heart failure flare-ups. *Med Sci Monit*. 2016;22:3614–3622. https://doi.org/10.12659/MSM.897529.
19. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, et al.. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Hear J*. 2004;147:331–338. https://doi.org/10.1016/j.ahj.2003.08.012.
20. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). *Biometrika*. 1965;52:591–611. https://doi.org/10.1093/biomet/52.3-4.591.
21. Razali NM, Wah YB. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. *J Stat Model Anal*. 2011;2:21–33.
22. Doane DP, Seward LE. Measuring skewness: a forgotten statistic? *J Stat Educ*. 2011;19:1–18.
23. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al.. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:e240–327. https://doi.org/10.1161/CIR.0b013e31829e8776.
24. Brandimarte F, Mureddu GF, Boccanelli A, Cacciatore G, Brandimarte C, Fedele F, et al.. Diuretic therapy in heart failure: current controversies and new approaches for fluid removal. *J Cardiovasc Med*. 2010;11:563–570. https://doi.org/10.2459/JCM.0b013e3283376bfa.
25. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev 2005:CD003178. http://doi.org/10.1002/14651858.CD003178.pub3.
26. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol*. 1996;28:376–382. https://doi.org/10.1016/0735-1097(96)00161-1.
27. Llorens P, Miro O, Herrero P, Martin-Sanchez FJ, Jacob J, Valero A, et al.. Clinical effects and safety of different strategies for administering intravenous diuretics in acutely decompensated heart failure: a randomised clinical trial. *Emerg Med J*. 2014;31:706–713. https://doi.org/10.1136/emermed-2013-202526.
28. Palazzuoli A, Pellegrini M, Ruocco G, Martini G, Franci B, Campagna MS, et al.. Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial. *Crit Care*. 2014;18:R134. https://doi.org/10.1186/cc13952.
29. Vijayaraghavan Kris, Crum Sue, Cherukuri Sangita, Barne-Avery Leslie. Association of impedance cardiography parameters with changes in functional and quality-of-life measures in patients with chronic heart failure. *Congest Heart Fail*. 2004;10(2 Suppl 2):22–27. https://doi.org/10.1111/j.1527-5299.2004.03408.x.
30. Strobeck John E, Silver Marc A. Beyond the four quadrants: the critical and emerging role of impedance cardiography in heart failure. *Congest Hear Fail*. 2004;10(s2):1–6. https://doi.org/10.1111/j.1527-5299.2004.03405.x.
31. Springfield Charles L, Sebat Frank, Johnson David, Lengle Steven, Sebat Christian. Utility of impedance cardiography to determine cardiac vs. noncardiac cause of dyspnea in the emergency department. Congest Heart Fail 2004;10(2 Suppl 2):14–6. http://doi.org/10.1111/j.1527-5299.2004.03409.x.
32. Rajput R, Das S, Chauhan S, Bisoi A, Vasdev S. Comparison of cardiac output measurement by noninvasive method with electrical cardiometry and invasive method with thermodilution technique in patients undergoing coronary artery bypass grafting. *World J Cardiovasc Surg*. 2014;4:123–130. https://doi.org/10.4236/wjcs.2014.47019.
33. Malik V, Subramanian A, Chauhan Hote S, Hote. Correlation of electric cardiometry and continuous thermodilution cardiac output monitoring systems. *World J Cardiovasc Surg*. 2014;4:101–108. https://doi.org/10.4236/wjcs.2014.47016.
34. Malfatto Gabriella, Blengino Simonetta, Perego Giovanni B, Branzi Giovanna, Villani Alessandra, Facchini Mario, et al.. Transthoracic impedance accurately estimates pulmonary wedge pressure in patients with decompensated chronic heart failure. *Congest Hear Fail*. 2012;18(1):25–31. https://doi.org/10.1111/j.1751-7133.2011.00248.x.
35. Velazquez-Cecena JL, Sharma S, Nagajothi N, Khraisat A, Khosla S, Arora RR, et al.. Left ventricular end diastolic pressure and serum brain natriuretic peptide levels in patients with abnormal impedance cardiography parameters. *Arch Med Res*. 2008;39(4):408–411. https://doi.org/10.1016/j.arcmed.2007.12.010.
36. van Meyel JJ, Smits P, Dormans T, Gerlag PG, Russel FG, Gribnau FW. Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance. *J Intern Med*. 1994;235:329–334.
37. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. *J Card Fail*. 2010;16:188–193. https://doi.org/10.1016/j.cardfail.2009.11.005.
38. Copeland JG, Campbell DW, Plachetka JR, Salomon NW, Larson DF. Diuresis with continuous infusion of furosemide after cardiac surgery. *Am J Surg*. 1983;146:796–799.
39. Pang PS, Konstam MA, Krasa HB, Swedberg K, Zannad F, Blair JE, et al.. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. *Eur Hear J*. 2009;30:2233–2240. https://doi.org/10.1093/eurheartj/ehp253.
40. Aspromonte N, Cruz DN, Valle R, Bonello M, Tubaro M, Gambaro G, et al.. Metabolic and toxicological considerations for diuretic therapy in patients with acute heart failure. *Expert Opin Drug Metab Toxicol*. 2011;7:1049–1063. https://doi.org/10.1517/17425255.2011.586629.
41. Klinge JM, Scharf J, Hofbeck M, Gerling S, Bonakdar S, Singer H. Intermittent administration of furosemide versus continuous infusion in the postoperative management of children following open heart surgery. *Intensive Care Med*. 1997;23:693–697.