ORIGINAL RESEARCH ARTICLE

Continuous versus intermittent use of furosemide in patients with heart failure and moderate chronic renal dysfunction

Zhigui Zheng* [ID], Xinxin Jiang, Jianguo Chen, Dongyuan He, Xiaohui Xie and Yunan Lu

Department of Nephrology, Zhejiang Hospital, Gudun Road 1229, Hangzhou, Zhejiang Province, China

Abstract

Aims   There is paucity of clinical data comparing continuous infusion (CI) with bolus injection (BI) of intravenous loop diuretics in patients with acute decompensated heart failure (ADHF) and chronic renal dysfunction. This study aimed to compare the efficacy and safety of CI versus BI intravenous furosemide administration in patients with ADHF and moderate chronic renal insufficiency.

Methods and results   Acute decompensated heart failure and moderate chronic renal insufficiency [with estimated glomerular filtration rate (eGFR) 15.0–44.9 mL/min/1.73 m^2] were randomized to start intravenous furosemide by BI or by a 6 h CI. End points included freedom from congestion at 72 h, the degree of dyspnoea assessed using the 0–10 Borg's category ratio scale, net daily urine output, weight loss during the study, length of hospital stay, total urinary sodium excretion, and development of acute kidney injury or electrolyte disturbance. After 72 h of treatment, the rate of the primary endpoint of freedom from congestion in the CI group was significantly higher than that in the BI group (69.05% vs. 43.59%, *P* = 0.02). The modified Borg scale indicated patients in the CI group had lower dyspnoea score than those in the BI group at 48 h (4.29 ± 1.23 vs. 5.97 ± 1.56; *P* = 0.02) and 72 h (1.15 ± 0.35 vs. 2.66 ± 0.83; *P* = 0.003). There were other significant differences favouring the CI group with regard to net urine output at 72 h (5145.98 ± 621.37 mL vs. 3755.95 ± 456.93 mL; *P* = 0.007), the mean body weight loss (4.72 ± 1.01 kg vs. 3.53 ± 0.73 kg; *P* = 0.02) and the total urinary sodium excretion (385.05 ± 38.15 vs. 320.33 ± 37.67; *P* = 0.02). The length of hospitalization in the CI group was significantly shorter than that in the BI group (10.36 ± 4.20 days vs. 15.68 ± 6.15 days; *P* = 0.02). No significant differences were observed between groups in the frequency of acute kidney injury, tinnitus, electrolyte disturbance or mortality.

Conclusions   Continuous intravenous infusion of furosemide resulted in significantly greater diuresis than bolus administration of an equal dose in patients with moderate chronic renal insufficiency and ADHF, while no differences emerged in terms of side effects or mortality.

Introduction

Acute decompensated heart failure (ADHF) may occur due to decreased glomerular filtration and salt and water retention when chronic kidney disease (CKD) with various causes progresses to renal insufficiency, which is also known as type 4 cardiorenal syndrome.[1] The cornerstone of therapy for ADHF is decreasing congestion through diuresis. However, diuretic resistance is a very common issue in acute heart failure and

is strongly associated with underlying lower GFR.[2,3] To maintain high concentrations of furosemide delivery in the proximal renal tubule to allow it to effectively act as a Na-K-2CL transporter on the luminal side of the thick ascending limb of the loop of Henle, optimizing the dose of furosemide is required when GFR is compromised.[2] Furthermore, several randomized, placebo-controlled clinical trials, although controversial, have concluded that continuous infusion of a loop diuretic may promote better diuresis than a bolus injection at

the same overall dose.[4–6] Possible explanations include constant urine output and less neurohormonal activation due to the continuous delivery rate of furosemide to the tubule and lower peak drug concentrations, which results in less change in intravascular volume and fewer incidents of severe side effects. However, there is a paucity of clinical data regarding the efficacy and safety of continuous furosemide infusion therapy in patients with chronic renal insufficiency.[7] Hence, we performed the present study to compare the efficacy and safety of continuous infusion with bolus intravenous furosemide administration in patients with congestive heart failure and moderate chronic renal insufficiency.

Methods

Study design, participants, and intervention

This was a prospective, randomized controlled clinical trial conducted by the Nephrology Department of Zhejiang Hospital in China. After receiving approval from the hospital ethics committee, adult patients (18–90 years) admitted to the hospital for Class III-IV ADHF (New York Heart Association classification) with moderate chronic renal insufficiency (eGFR 15.0–44.9 mL/min/1.73 m^2) were selected for inclusion in the study between June 2016 and July 2019. Patients were excluded from the study for the following reasons: history of allergies to furosemide, acute kidney injury before enrolment, other causes of heart failure including acute decompensated chronic heart failure and chronic heart failure requiring medications' dose-adjustments, renal replacement therapy prior to hospitalization or during the 72 h treatment, adjustment of dosing strategy of furosemide in any group or addition of other diuretics or other medication known to influence urine volume during the treatment. All patients provided written informed consent.

According to eGFR, the patients were categorized into two groups: group A (30.0–44.9 mL/min/1.73 m^2) and group B (15.0–29.9 mL/min/1.73 m^2). The fixed dose of furosemide was 160 mg per day for group A and 200 mg per day for group B according to the ceiling dose for the respective eGFR.[8] The patients were randomized to receive the fixed total dose of furosemide either as an intravenous bolus injection (BI) within 5 min every day or a 6 h intravenous continuous infusion (CI). Randomization was performed using the sequentially numbered cases by computer-generated scheme. Furosemide was diluted in 50 mL of 0.9% sodium chloride for both groups. To prevent potential confounders related to the administration, we did not use the preceding loading dose in the CI group. Daily 24 h urine was collected for three consecutive days after the start of furosemide administration for the measurement of the volume and concentrations of sodium, potassium, and creatinine. At admission,

medical history and anthropometric parameters were recorded for all patients. Blood tests for complete blood count, electrolytes, creatinine, and urea nitrates were performed at baseline and repeated daily for the first 3 days after admission. The primary outcome was freedom from congestion at 72 h (defined as jugular venous pressure of <8 cm without orthopnoea and with trace peripheral oedema or no oedema). The degree of dyspnoea was assessed by study participants using the 0–10 Borg's category ratio scale.[9] Secondary outcomes included net daily urine output, weight loss during the study, total urinary sodium excretion, and length of hospital stay. Adverse events such as tinnitus, development of acute kidney injury, and electrolyte disturbances during the treatment period were also recorded. All analyses were conducted on an intention-to-treat basis. The eGFR was calculated by the modification of diet in renal disease (MDRD) formula.

Statistical methods

Statistical analyses were performed using SPSS version 18.0. Continuous variables are expressed as the mean ± SD, and categorical variables are presented as percentages. We used Kolmogorov–Smirnov tests to examine the normality of the distributions of quantitative variables. Student's t test was used to compare the means of normally distributed variables, while the Mann–Whitney U test was used to compare not normally distributed variables between the two groups. Differences in the categorical variables were analysed by the χ^2 test. A P-value <0.05 was considered statistically significant.

Results

Figure 1 shows a flow chart of the participants through the study. Eight patients in the BI group and five in the CI group dropped out because of undergoing renal replacement or dose adjustment during the intervention. After exclusion, a total of 81 patients were included in this study and finally finished the 72 h protocol. The mean age of the population was 66.46 ± 8.21 years, the mean weight was 57.56 ± 8.82 kg, and 53 (65.43%) were men. There were no significant differences in baseline demographic, clinical or biochemical characteristics between the two groups (Table 1).

After 72 h of treatment, the rate of the primary endpoint of freedom from congestion in the CI group was significantly higher than that in the BI group (69.05% vs. 43.59%, $P = 0.02$, Table 2), although the differences were not statistically significant in comparisons of two subgroup analysis. The results of modified Borg scale during the intervention demonstrated that patients in the CI group had lower dyspnoea score than those in the BI group at 48 h (4.29 ± 1.23 vs. 5.97 ± 1.56;

Figure 1 Flow chart of the participants through the study. CI, continuous infusion; BI, bolus injection.
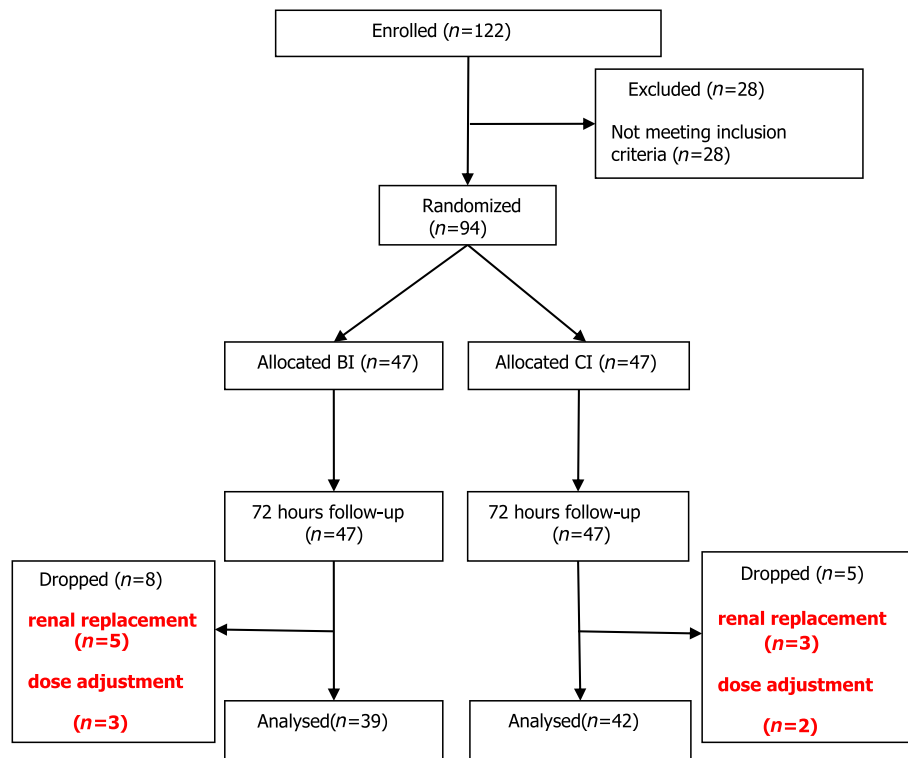
P = 0.02; *Figure 2*) and 72 h (1.15 ± 0.35 vs. 2.66 ± 0.83; *P* = 0.003; *Figure 2*). As shown in *Table 2*, body weight loss between the two groups was also found to be significantly different. Greater reductions from baseline in mean body weight were also observed in CI group at 48 h (−3.46 ± 0.63 vs. −2.36 ± 0.57; *P* = 0.03; *Figure 3*) and 72 h (−4.72 ± 1.01 vs. −3.53 ± 0.73; *P* = 0.02; *Figure 3*). The length of hospitalization in the CI group was significantly shorter than that in the BI group (10.36 ± 4.20 days vs. 15.68 ± 6.15 days; *P* = 0.02; *Table 2*). However, a difference in the reduction in BNP between the two groups was not detected (536.28 ± 167.92 pg/mL vs. 488.35 ± 190.74 pg/mL; *P* = 0.08; *Table 2*).

Diuretic response, including total net urinary output and total urinary sodium excretion, was higher in the CI group than those in the BI group (*P* = 0.01 and *P* = 0.02, respectively). *Figure 4* shows the cumulative net urinary output at 72 h of treatment in the two groups. At the end of 48 h of treatment, a difference in urine volume between the CI group and BI group was observed (*P* = 0.01), the trend of which was even pronounced at 48 and 72 h of treatment. *Figure 5* displays the daily cumulative urinary sodium excretion during the 72 h treatment. The indicator shows similar results: as the treatment continued, the difference between the two groups became more significant.

With regard to the safety end point, no patient died during hospitalization in either group. There were no significant differences in changes in the serum creatinine level, blood pressure, heart rate, potassium level or sodium level from baseline to 72 h between groups (*Table 2*). The change in cumulative urinary potassium excretion at 72 h of treatment is revealed in *Figure 6*. No statistically significant differences were found at the end of the three time points of treatment between the two groups. In addition, no differences emerged in terms of the prevalence of hyponatraemia, hypokalaemia, hypomagnesium, tinnitus, acute kidney injury or hypotension during the intervention phase (*Table 2*).

Discussion

One of the major determinants of the natriuretic response of furosemide is the rate of drug delivery into the nephron.[10] It is widely accepted that patients with chronic renal insufficiency have low renal blood flow due to decreased numbers of functioning nephrons. In addition, the accumulated endogenous organic acids of azotaemia block the secretion of furosemide into the lumen at the proximal tubule.[11,12] These combined effects abate the amount of loop diuretics that

Table 1 Baseline characteristics of the study participants

Variable	CI group ($n = 42$)	BI group ($n = 39$)	P value
Age (years)	65.53 ± 7.84	67.38 ± 8.57	0.38
Male sex, n (%)	28 (66.67)	25 (64.10)	0.81
Body weight (kg)	58.65 ± 9.25	56.47 ± 8.39	0.32
Cause of CKD, n (%)			
Chronic glomerulonephritis	8 (19.05)	10 (25.64)	0.46
Diabetic nephropathy	17 (40.48)	15 (38.46)	0.65
Hypertensive nephropathy	13 (30.95)	10 (25.64)	0.60
Obstructive nephropathy	3 (7.14)	5 (12.82)	0.39
Other causes	2 (4.76)	3 (7.69)	0.93
Group A	16 (38.10)	17 (43.59)	0.62
Group B	26 (61.90)	22 (56.41)	0.62
Hypertension, n (%)	40 (95.24)	36 (92.31)	0.93
Coronary heart disease, n (%)	8 (19.05)	5 (17.95)	0.45
Valvular heart disease, n (%)	5 (11.90)	6 (15.38)	0.65
Cardiomyopathy, n (%)	3 (7.14)	2 (5.13)	0.93
Diabetes mellitus, n (%)	21 (50.00)	17 (43.59)	0.56
Dyslipidaemia, n (%)	15 (35.71)	12 (30.77)	0.64
Cerebrovascular disease, n (%)	10 (23.81)	7 (17.95)	0.52
Atrial fibrillation, n (%)	8 (19.05)	5 (12.82)	0.51
NYHA classification, n (%)			
III	32 (76.19)	33 (84.62)	0.34
IV	10 (23.81)	6 (15.38)	0.34
Systolic blood pressure (mmHg)	156.72 ± 21.43	160.41 ± 24.93	0.27
Diastolic blood pressure (mmHg)	95.44 ± 15.09	96.72 ± 16.43	0.31
Heart rate	91.45 ± 15.22	92.78 ± 13.09	0.58
Cold and wet profile, n (%)	5 (11.90)	5 (12.82)	0.90
Warm and wet profile, n (%)	37 (88.10)	34 (87.18)	0.90
Laboratory and echo-Doppler data			
Haemoglobin(g/L)	92.28 ± 9.03	89.75 ± 7.11	0.15
Serum creatinine (μmol/L)	203.36 ± 36.91	201.55 ± 35.01	0.57
eGFR (MDRD) (mL/min/1.73 m^2)	28.38 ± 14.06	30.86 ± 16.98	0.28
Serum BUN (mmol/L)	22.18 ± 6.75	25.76 ± 10.55	0.13
Serum sodium (mmol/L)	130.72 ± 4.26	132.56 ± 5.90	0.58
Serum potassium (mmol/L)	4.87 ± 1.26	4.76 ± 1.13	0.33
BNP (pg/mL)	1385.61 ± 228.39	1421.89 ± 1.26	0.28
LVEF(%)	56.12 ± 10.92	58.80 ± 11.24	0.24
Type of heart failure			
Left heart failure, n (%)	35 (83.33)	32 (82.05)	0.88
Right heart failure, n (%)	5 (11.90)	6 (15.38)	0.65
Biventricular heart failure, n (%)	2 (4.76)	1 (2.56)	0.95
X-ray			
Pulmonary oedema, n (%)	32 (76.19)	28 (71.79)	0.65
Pulmonary congestion, n (%)	8 (19.05)	9 (23.08)	0.66
Pleural effusion, n (%)	6 (14.29)	8 (20.51)	0.46

Values are mean ± SEM.
BI, bolus injection; BNP, B-type natriuretic peptide; CI, continuous infusion; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

can be delivered into the tubule to reach its site of action. Thus, although the response of the remaining nephrons to furosemide in patients with renal insufficiency is normal, large doses are still needed to obtain a high serum concentration, thereby providing adequate amounts of diuretic into the urine. Another factor that may influence the diuretic response is the time course of the delivery of furosemide into the proximal tubule.[10] Joseph et al.[13] found that continuous infusion of furosemide was superior to bolus administration in healthy volunteers with regard to diuretic efficiency. Nonetheless, whether the results are similar among patients with congestive heart failure remains an ongoing issue, and there is a paucity of relevant data involving patients with chronic renal insufficiency.[7,11,12]

Based on the prospective and randomized clinical trial, we found that the continuous administration of furosemide results in faster decongestion and greater diuresis than intermittent bolus injection in patients with severe chronic renal insufficiency and congestive heart failure. The length of hospitalization was also significantly shortened by the adoption of this strategy. To our knowledge, this is the study with the largest sample size comparing continuous and bolus administration of an equal dose of furosemide in patients with severe renal insufficiency.

There are still controversies regarding differences in the efficacy and safety of continuous infusion vs bolus injection of intravenous loop diuretics in patients with acute decompensated heart failure. Most clinical trials favoured the mode of

Table 2 Endpoints

| Variable	CI group (n = 42)	BI group (n = 39)	*P* value
Freedom from congestion, n(%)	29 (69.05)	17 (43.59)	0.02
Group A	11 (68.75)	7 (41.18)	0.11
Group B	18 (69.23)	10 (45.45)	0.10
Body weight loss (kg)	4.72 ± 1.01	3.53 ± 0.73	0.02
Total net urinary output (mL)	5145.98 ± 621.37	3755.95 ± 456.93	0.01
Total urinary sodium excretion (mmol)	385.05 ± 38.15	320.33 ± 37.67	0.02
Average of FeNa (%)	7.36 ± 3.32	5.03 ± 2.49	0.14
Length of hospitalization (days)	10.36 ± 4.20	15.68 ± 6.15	0.02
Mean change in systolic blood pressure (mmHg)	−18.58 ± 7.59	−15.00 ± 5.44	0.08
Mean change in diastolic blood pressure (mmHg)	−7.92 ± 8.03	−6.46 ± 6.49	0.11
Mean change in heart rate	−12.66 ± 7.70	−10.92 ± 8.79	0.26
Mean change in BNP (pg/mL)	−536.28 ± 167.92	−488.35 ± 190.74	0.08
Mean change in creatinine (μmol/L)	18.36 ± 10.20	20.58 ± 7.53	0.12
Mean change in serum potassium (mmol/L)	−0.23 ± 0.39	−0.28 ± 0.48	0.47
Mean change in serum sodium (mmol/L)	−3.58 ± 2.59	−2.72 ± 3.15	0.28
Total urinary potassium excretion (mmol)	163.11 ± 30.04	198.57 ± 52.49	0.08
Hyponatraemia, *n* (%)	8 (19.05)	5 (12.82)	0.45
Hypokalaemia, *n* (%)	10 (23.81)	7 (17.95)	0.52
Hypomagnesium, *n* (%)	12 (28.57)	9 (23.08)	0.57
Tinnitus, *n* (%)	1 (2.38)	3 (7.69)	0.56
Acute kidney injury, *n* (%)	7 (16.67)	9 (23.08)	0.47
Hypotension, *n* (%)	5 (11.90)	3 (7.69)	0.53

Values are mean ± SEM.
BI, bolus injection; BNP, B-type natriuretic peptide; CI, continuous infusion; FeNa, fractional excretion of natrium.

Figure 2 Patients' subjective symptoms of dyspnoea using the modified Borg scale. CI, continuous infusion; BI, bolus injection.
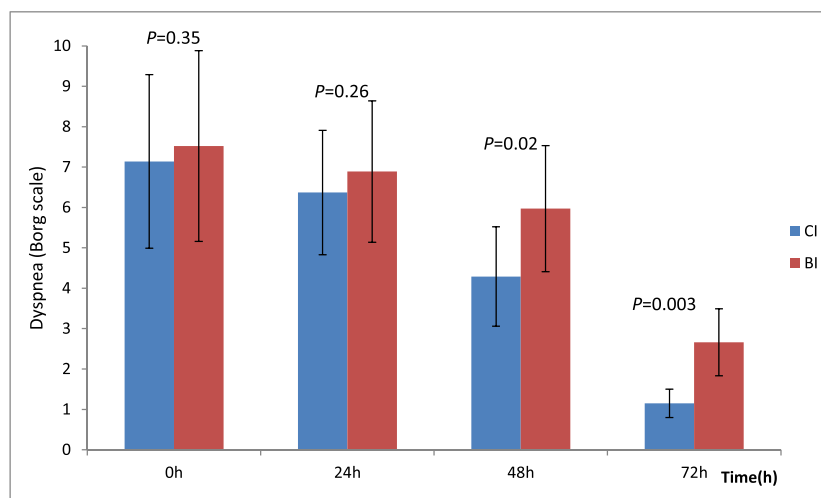

continuous infusion in terms of diuretic effect.[4,6,14–16] A variety of mechanisms may be involved in this process. First, the approach of continuous infusion may attenuate the possibility of acute postdiuretic compensatory sodium reabsorption. Second, continuous infusion could provide more constant and gradual diuresis with less neurohormonal activation, leading to lower fluctuations in intravascular volume.[17] Third, lower peak plasma concentrations are theoretically correlated with less frequent toxic side effects.[18,19] When renal function is compromised, the situation becomes even more complicated. Although the pharmacodynamics of the

response to furosemide in patients with renal insufficiency seem normal, the lower amount of filtered sodium diminishes the interaction between the diuretic and tubular solute reabsorption.[20] In a prospective randomized crossover study by Sanjay *et al*.,[7] a total of 42 patients with chronic renal insufficiency were recruited. The researchers reported that continuous furosemide infusion was associated with greater natriuretic and diuretic effects than bolus administration. Another clinical trial focused on the two types of administration of bumetanide in treating patients with severe chronic renal dysfunction and drew a similar conclusion.[12] Our findings

Figure 3 Change in weight between groups. CI, continuous infusion; BI, bolus injection.
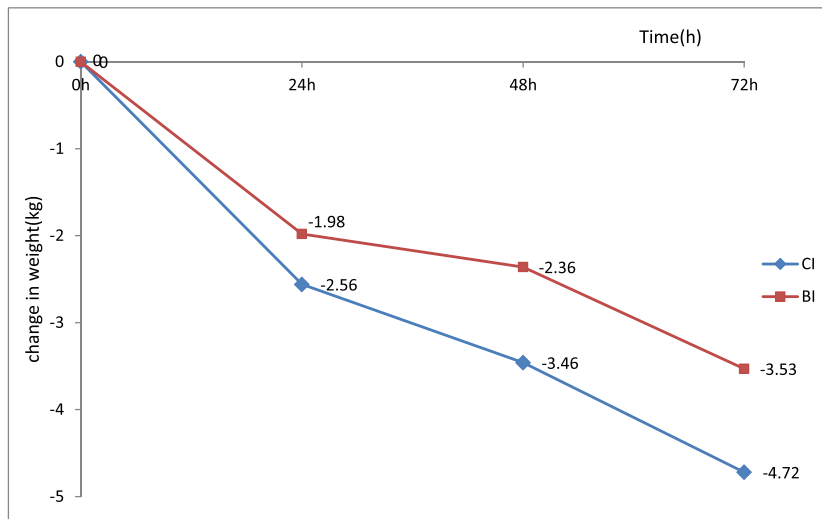
Figure 4 Cumulative net urinary output between groups. CI, continuous infusion; BI, bolus injection.
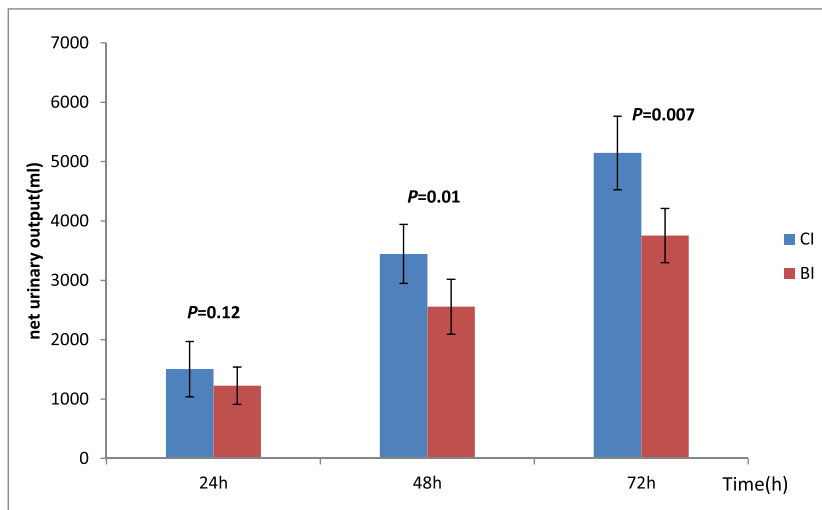

were largely congruent with the two aforementioned studies. Nonetheless, much more data from other studies are needed to validate the theory.

However, In a large prospective, double-blind, randomized Diuretic Optimization Strategies Evaluation (DOSE) trial,[21] no significant difference in the patients' global assessment was found between the two types of furosemide administration. There are some limitations to this study. First, the trial population was enrolled without consideration of resistance to diuretics, which could be a confounding variable in the final result. In addition, their study mainly focused on patients with normal kidney function, so the conclusion may not generalize to those with renal insufficiency. In addition, the trial allowed for adjustments to the diuretic dosing strategy by the treating physician after 48 h, which may bias the final conclusion. Another clinical trial by Larry et al.[18] did not detect a difference between the two types of administration of loop diuretics. However, there was insufficient power to draw statistically significant conclusions due to the smaller sample size, and the results were not applicable to patients with chronic renal dysfunction.

In contrast to previous studies,[22,23] we did not apply the loading dose preceding the continuous infusion of furosemide. According to the previous literature, only when accompanied by a loading dose can the administration of continuous infusion show a superior diuretic effect.[22]

Figure 5 Cumulative urinary sodium excretion between groups. CI, continuous infusion; BI, bolus injection.
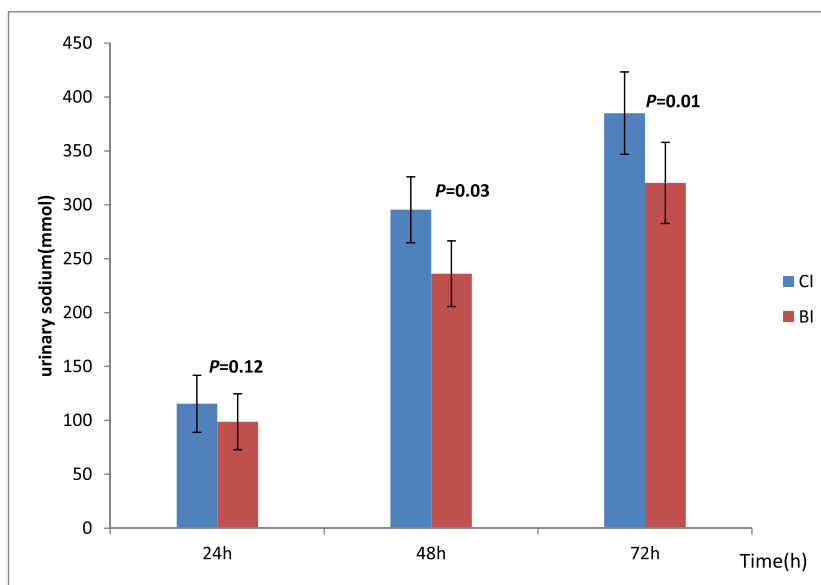
Figure 6 Cumulative urinary potassium excretion between groups. CI, continuous infusion; BI, bolus injection.
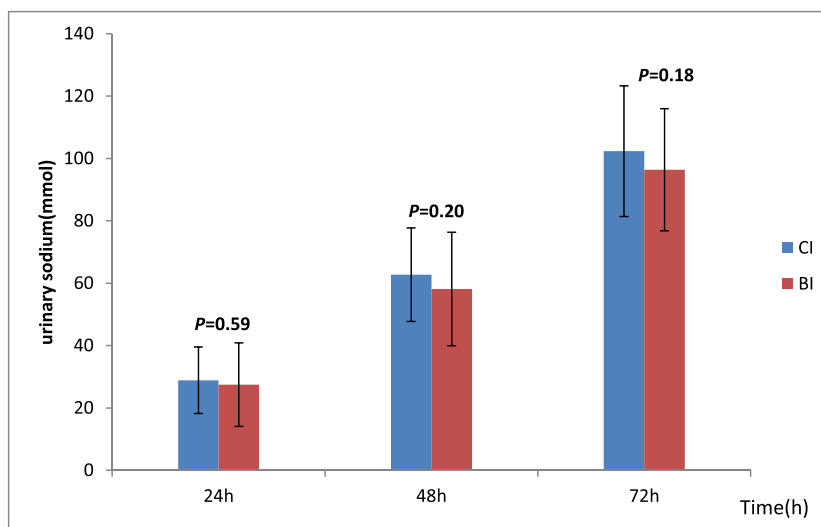
However, the same conclusion we came to supports the effectiveness of continuous infusion of furosemide without the administration of a loading dose. The onset of diuresis may be delayed without the loading dose, but we did not find an impact on the final efficacy. The possible explanation might be that the average dose per unit time achieved by continuous infusion increased accordingly due to the absence of the loading dose with the unchanged total dose. Of note, the loading dose itself can be a potential confounding factor

that may influence the outcome of the comparison of the two modes of administration. Thus, it remains an ongoing issue that needs to be further explored.

Two other issues deserve more attention. First, there is currently a lack of a universally accepted criterion for precisely defining 'continuous', which could range from 8 to 24 h per day.[5,16,24] We observed that the continuous intravenous infusion of loop diuretics for 6 h was also superior to bolus administration. Our setting for the duration of the

continuous intravenous infusion is much shorter than those used in previous studies. Although the study focused exclusively on patients with chronic renal dysfunction, the final positive outcome reminds us that the administration of 6 h continuous infusion may also be an alternative mode for patients without renal insufficiency. A direct benefit it could bring is a reduction in nurses' workload to some extent. In addition, our study was not designed as a crossover trial. Although the design did not allow for heterogeneity between groups to be avoided, it may reduce the potential effect on the outcomes generated by the lack of an adequate washout period. Further large-scale multicentre studies certainly need to be performed to offer more related data.

In terms of adverse effects, our study revealed nonsignificant differences in the proportion of acute renal injury, hypotension, hyponatraemia, hypokalaemia, hypomagnesium, and tinnitus between the two strategies of intravenous furosemide administration, a finding that is in accordance with most previous literature.[4,14,25] It is well established that intravascular volume depletion caused by high-dose loop diuretics may theoretically lead to haemodynamic changes, hypotension, renal dysfunction, and electrolyte disturbances.[26,27] However, intravascular volume overload in patients with cardio-renal syndrome is often associated with renal venous congestion, which may worsen renal function.[28] Thus, reducing renal vein pressure by continuous infusion of furosemide itself is expected to improve renal function rather than worsen it. In addition, reduced glomerular filtration may also influence the excretion of electrolytes, which makes the incidence of hypokalaemia and hypomagnesium decrease. To prevent adverse effects, close monitoring of kidney function and electrolyte imbalance during the administration of furosemide is still recommended to allow for the early correction of abnormalities.

Three limitations of this study should be acknowledged. First, the study was conducted at a single medical institution and was not blinded, which may produce potential bias. Second, although patients with dosing adjustment of furosemide during the intervention period were excluded, the use of previous oral or intravenous diuretics in patients with congestive heart failure prescribed by other physicians before enrolment was not excluded, which may interfere with the results. Third, we did not conduct a follow-up of confirming whether long-term use of continuous infusion of furosemide may better delay the time of entering renal replacement and improve the prognosis.

Conclusion

Our study demonstrates that continuous intravenous infusion of furosemide without preceded bolus injection results in significantly greater diuresis than bolus administration of the equal dose in patients with advanced chronic renal insufficiency and congestive heart failure. The findings also indicate that continuous infusion of furosemide is not correlated with an adverse effect on renal function, electrolyte disorders or mortality. Thus, continuous infusion of furosemide may be a more appropriate option than bolus injection to achieve better natriuresis in patients with congestive heart failure and moderate chronic renal insufficiency.

Conflict of interest

None declared.

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