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COMPARISON OF THE OUTCOME OF CONTINUOUS INFUSION VERSUS INTERMITTENT BOLUS DOSING OF FUROSEMIDE IN ACUTE HEART FAILURE PATIENTS

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ABSTRACT

Background and Objectives: *Acute heart failure often need intravenous furosemide; however the ideal method of administration is still contested. Continuous infusion may confer renal protection by maintaining steady medication levels, whereas intermittent bolus may yield enhanced diuresis. Our study objectives are 1) to compare the mean serum creatinine levels and BUN levels 2) to compare mean urine output, eGFR and BNP following continuous infusion versus intermittent bolus dosing of furosemide in acute heart failure patients.*

Methodology: *This prospective, randomized trial enrolled 60 ADHF patients (NYHA Class III-IV, LVEF <50%) at a tertiary cardiac center of Rawalpindi from January to June 2025. Patients of continuous infusion group received furosemide infusion at a dose of 2-3mg/h and intermittent group patients received furosemide at a dose of 40mg every 8hours. All patients received protocolized fluid/electrolyte monitoring. Primary endpoints included 72-hour change in renal function (creatinine and BUN) while, secondary endpoints comprised BNP reduction, urine output and eGFR. Data was evaluated using IBM-SPSS Version 25. Mean values of primary and secondary outcomes were compared using t-test and $p \leq 0.05$ considered significant.*

Results. *Continuous infusion demonstrated superior renal protection, with significantly lower creatinine (1.33 ± 0.66 vs. 1.78 ± 0.50 mg/dL; p=0.004) and BUN levels (18.32 ± 7.63 vs. 36.40 ± 20.47 mg/dL; p<0.001). Intermittent bolus yielded higher urine output (2718.90 ± 829.83 vs. 2078.18 ± 429.73 mL, p<0.001). Although not statistically significant (p=0.110), a trend indicating a higher eGFR (61.63 ± 11.14 vs 53.70 ± 24.31 mL/min/1.73m²) further corroborated the renal advantages of continuous infusion.*

Conclusions*: Continuous furosemide infusion offers superior renal protection, while intermittent bolus provides more robust diuresis. Treatment selection should consider patient-specific factors, such as age, comorbidities, and symptom duration. These findings support personalized decongestion strategies in AHF.*

KEY WORDS: *furosemide, infusion, acute, heart failure, creatinine, urine output, glomerular filtration rate.*

INTRODUCTION

Acute heart failure (AHF) is a critical clinical illness marked by a swift decline in cardiac function due to structural and/or functional cardiac abnormalities, resulting in considerable morbidity and mortality. The incidence of heart failure differs by geography and demographic group.[i] In advanced nations, the prevalence of AHF ranges from 1.5% to 2.0% within the general population, while the incidence among individuals over 70 exceeds 10%.[ii] Research indicates that AHF imposes a significant economic strain on

families and society due to emergency admissions, readmissions, and extended hospital stays.[iii]

Fluid retention and congestion account for 90% of heart failure hospitalisations, with increased severity of congestion correlating with poorer outcomes.[iv] Intravenous (IV) loop diuretics are a mainstay of the pharmacological treatment of AHF. Intravenous (IV) loop diuretics are a cornerstone of the pharmaceutical management of acute heart failure (AHF). Despite the widespread utilisation of these medicines, questions regarding optimal dose and overall safety profile remain persist.[v] Consequently, clinical practice exhibits significant variability among locations and nations concerning both delivery methods and dose regimens. Theoretically, continuous infusion of a loop diuretic, by maintaining steady blood levels, should facilitate more sustained diuresis, hence preventing significant fluctuations in intravascular volume and subsequent neurohormonal activation.[vi,vii] Continuous intravenous infusion with adequate dose may avoid the attainment of elevated or hazardous levels, hence resulting in fewer and less severe adverse effects. [viii]

Theoretically continuous infusion is preferred over intermittent bolus since it provide gradual diuresis with reduced neuro-hormonal activation. Continuous infusion of furosemide prevents occurrence of rebound sodium i.e. when large amount of sodium, potassium and water are eliminated from the body, it may lead to hyponatremia which forces the immediate absorption of the sodium back into the blood leading to sodium imbalance which usually occurs with intermittent bolus. Since continuous infusion provides gradual diuresis, occurrence of rebound sodium is less initiated, hence it is preferred in pulmonary oedema. On searching the literature, very limited data is available and also no such local study is available. The results of this study will not only provide us with the local data but will also help the clinicians for better recommendation of furosemide dose in order to improve the outcome.

MATERIALS AND METHODS

This research employed a randomised controlled trial (RCT) methodology to evaluate the effectiveness of continuous infusion compared to intermittent bolus administration of furosemide in individuals with acute heart failure (AHF). The study was carried out in the Department of Cardiology at Fauji Foundation Hospital, Rawalpindi, over a six-month duration from January 2025 to June 2025. The sample size was determined utilising the WHO sample size calculator, employing a 5% significance level ($\alpha = 0.05$) and 80% power ($\beta = 0.20$), informed by prior data indicating mean serum creatinine levels of 1.73 ± 0.52 mg/dl in the continuous infusion group versus 1.18 ± 0.68 mg/dl in the intermittent bolus group (according to the findings of Shree J et al.). The computation established that 60 patients (30 per group) are adequate for significant statistical analysis. Non-probability, consecutive sampling was employed to recruit eligible participants.

Participants in the study were aged 25 to 70 years, of either sex, and diagnosed with acute heart failure (LVEF <50% on echocardiogram accompanied by sudden-onset dyspnoea). The exclusion criteria comprised persons with chronic kidney disease, recent haemorrhage, stroke, chest wall trauma (within 40 days), or a history of cardiothoracic surgery, coronary artery bypass grafting (CABG), or acute pulmonary embolism. Operational definitions were standardised for consistency: hypertension was defined as controlled blood pressure (<140/90 mmHg on two readings 8 hours apart) in patients undergoing treatment for ≥2 years, while diabetes mellitus was defined as controlled fasting blood sugar (<110 mg/dl on two readings 8 hours apart) in patients receiving treatment for ≥2 years. The Body Mass Index (BMI) was computed using height and weight (kg/m^2).

Upon obtaining ethical permission and informed consent, baseline data encompassing demographics (age, gender), clinical history (diabetes, hypertension), and anthropometric measurements (height, weight, BMI) were documented. Patients were subsequently randomised using a random number table into two groups: Group I (continuous furosemide infusion at 2-3 mg/hour) and Group II (intermittent bolus dose at 40 mg every 8 hours). After 24 hours, the primary outcomes examined included urine output, serum creatinine, blood urea nitrogen (BUN), glomerular filtration rate (GFR), and B-type natriuretic peptide (BNP) levels. Urine production was documented in the ward, while blood samples were examined in the hospital laboratory by a seasoned consultant haematologist (≥3 years post-fellowship).

Statistical analysis was conducted with SPSS version 25.0. Continuous variables (e.g., age, laboratory values) will be expressed as mean ± standard deviation, whereas categorical variables (e.g., gender, diabetes) will be provided as frequencies and percentages. An independent samples t-test was employed to assess results between groups, with $p \leq 0.05$ being statistically significant. Potential confounding variables, including age, gender, BMI, diabetes, and

hypertension, were managed through stratification, succeeded by post-stratification t-tests where relevant, with $p < 0.05$ being statistically significant.

RESULTS

60 patients with acute heart failure were enrolled in this trial; they were split equally into two groups of 30 patients receiving intermittent boluses and continuous infusions. The intermittent group was slightly older (48.37 ± 12.64 years vs. 44.47 ± 13.96 years), with a mean age of 46.42 ± 13.35 years. BMI were nearly similar between groups (26.71 ± 5.52 vs. 27.03 ± 5.34 kg/m2) . T he intermittent group experienced the symptoms for a relatively longer period of time than continuous group (42.03 ± 20.13 vs. 36.90 ± 18.00 hours). The distribution of gender in both groups was comparable (53.3% male). The majority of patients (61.7%) were under 50 years old, and the proportion of patients who were overweight or obese (BMI ≥25 kg/m2, 61.7%) was marginally greater in the continuous group. The continuous infusion group had higher rates of diabetes (46.7% vs. 33.3%) and hypertension (60.0% vs. 46.7%). Tables 1 and 2 give a detailed descriptive quantitative and qualitative analysis for both study arms.

The continuous infusion group exhibited enhanced renal protection, evidenced by significantly reduced serum creatinine levels (1.33 ± 0.66 mg/dL vs 1.78 ± 0.50 mg/dL, p=0.004) and markedly reduced BUN levels (18.32 ± 7.63 mg/dL vs 36.40 ± 20.47 mg/dL, p<0.001), signifying improved kidney function and decreased azotemia. Although not statistically significant (p=0.110), a trend indicating a higher eGFR (61.63 ± 11.14 vs 53.70 ± 24.31 mL/min/1.73m²) further corroborated the renal advantages of continuous infusion. In contrast, the intermittent bolus group attained a markedly higher urine output (2718.90 ± 829.83 mL versus 2078.18 ± 429.73 mL, p<0.001), indicating enhanced diuresis (table 3).

Stratification analysis indicated that females exhibit a more significant diuretic response to intermittent dose (854mL vs 454mL in men, p=0.002), although males demonstrated enhanced renal protective benefits from continuous infusion (BUN decrease p=0.007 versus p=0.002 in females). Patients aged ≤50 years exhibited enhanced renal protection with continuous infusion (BUN p=0.002), while those older than 50 demonstrated a substantial improvement in eGFR (p=0.018). Normal-weight individuals (<25kg/m²) exhibited the most pronounced diuretic response to intermittent dosage (818mL, p=0.011), whereas overweight patients demonstrated superior renal function with continuous infusion (Creatinine p=0.009). Early presenters (<24h) demonstrated improved eGFR preservation with continuous infusion (p=0.006), but late presenters (≥24h) attained enhanced diuresis with intermittent dosage (689mL, p<0.001). Non-hypertensives exhibited a superior diuretic response to intermittent dosage (953 mL, p=0.001). Table 4 elucidates the comprehensive stratification analysis.

Table 1: Mean and standard deviation for various quantitative demographic and clinical variables of both study groups

Variable	Group	N	Mean	Std. Deviation
Age (years)	Intermittent	30	48.37	12.64
	Continuous	30	44.47	13.96
	Total	60	46.42	13.35
Height (cm)	Intermittent	30	166.28	11.05
	Continuous	30	163.68	8.90
	Total	60	164.98	10.03
Weight (kg)	Intermittent	30	72.89	11.45
	Continuous	30	71.81	11.84
	Total	60	72.35	11.56
BMI (kg/m²)	Intermittent	30	26.71	5.52
	Continuous	30	27.03	5.34
	Total	60	26.87	5.38
Symptom Duration (hours)	Intermittent	30	42.03	20.13
	Continuous	30	36.90	18.00
	Total	60	39.47	19.11

Table 2: Frequency and percentages for various qualitative demographic and clinical variables of both study groups

Variable	Subgroup	Intermittent (n=30)	Continuous (n=30)	Total (n=60)
Sex	Male	16 (53.3%)	16 (53.3%)	32 (53.3%)
	Female	14 (46.7%)	14 (46.7%)	28 (46.7%)
Age Subgroup	≤50 years	18 (60.0%)	19 (63.3%)	37 (61.7%)
	>50 years	12 (40.0%)	11 (36.7%)	23 (38.3%)
BMI Subgroup	<25 kg/m²	12 (40.0%)	11 (36.7%)	23 (38.3%)
	≥25 kg/m²	18 (60.0%)	19 (63.3%)	37 (61.7%)
Symptom Duration	<24 hours	11 (36.7%)	10 (33.3%)	21 (35.0%)
	≥24 hours	19 (63.3%)	20 (66.7%)	39 (65.0%)
Hypertension	Yes	14 (46.7%)	18 (60.0%)	32 (53.3%)
	No	16 (53.3%)	12 (40.0%)	28 (46.7%)
Diabetes Mellitus	Yes	10 (33.3%)	14 (46.7%)	24 (40.0%)
	No	20 (66.7%)	16 (53.3%)	36 (60.0%)

Table 3: Comparison of primary and secondary outcomes among both study groups

Outcome	Intermittent Infusion (n=30)	Continuous Infusion (n=30)	p-value
Primary Outcomes			
Creatinine (mg/dL)	1.78 ± 0.50	1.33 ± 0.66	0.004
BUN (mg/dL)	36.40 ± 20.47	18.32 ± 7.63	<0.001
Secondary Outcomes			
Urine Output (mL)	2718.90 ± 829.83	2078.18 ± 429.73	<0.001
eGFR (mL/min/1.73m²)	53.70 ± 24.31	61.63 ± 11.14	0.110
BNP (pg/mL)	877.41 ± 593.58	921.05 ± 212.84	0.706

Table 4: Comparison of primary (Creatinine & BUN) outcomes among both study groups (stratification analysis)

Subgroup	Treatment	Urine Output (mL)	p-value	eGFR	p-value	BNP (pg/mL)	p-value
Male (n=32)	Intermittent	2558 ± 816	0.062	51.3 ± 28.2	0.175	904 ± 744	0.841
	Continuous	2105 ± 462		62.1 ± 13.4		943 ± 225	
Female (n=28)	Intermittent	2902 ± 837	0.002	56.5 ± 19.6	0.428	847 ± 380	0.676
	Continuous	2048 ± 405		61.1 ± 8.3		896 ± 203	
≤50 Years (n=37)	Intermittent	2712 ± 856	0.006	55.3 ± 29.2	0.572	767 ± 620	0.493
	Continuous	2066 ± 412		59.4 ± 10.8		874 ± 245	
>50 Years (n=23)	Intermittent	2729 ± 826	0.038	51.3 ± 15.1	0.018	1043 ± 535	0.812
	Continuous	2099 ± 480		65.5 ± 11.2		1003 ± 106	
BMI<25 kg/m^2 (n=23)	Intermittent	2898 ± 853	0.011	46.0 ± 26.0	0.109	917 ± 785	0.899
	Continuous	2080 ± 485		60.2 ± 10.6		885 ± 235	
BMI≥25 kg/m^2 (n=37)	Intermittent	2599 ± 816	0.018	58.8 ± 22.4	0.534	851 ± 448	0.429
	Continuous	2077 ± 409		62.5 ± 11.6		942 ± 203	
Duration of symptoms <24h (n=21)	Intermittent	2556 ± 1076	0.142	47.4 ± 19.0	0.006	741 ± 726	0.363
	Continuous	1987 ± 487		68.6 ± 10.8		959 ± 127	
Duration of symptoms ≥24h (n=39)	Intermittent	2813 ± 664	<0.001	57.3 ± 26.7	0.899	956 ± 507	0.671
	Continuous	2124 ± 404		58.2 ± 9.8		902 ± 246	
Hypertensive (n=32)	Intermittent	2519 ± 879	0.138	52.3 ± 30.7	0.252	940 ± 787	0.863
	Continuous	2170 ± 373		61.5 ± 11.5		906 ± 221	
Non-Hypertensive (n=28)	Intermittent	2894 ± 770	0.001	54.9 ± 18.0	0.247	823 ± 370	0.320
	Continuous	1941 ± 487		61.9 ± 11.0		943 ± 208	
Diabetic (n=24)	Intermittent	2373 ± 669	0.211	55.8 ± 14.9	0.096	871 ± 612	0.845
	Continuous	2096 ± 379		65.1 ± 11.2		906 ± 218	
Non- Diabetic (n=36)	Intermittent	2892 ± 863	0.002	52.6 ± 28.2	0.429	881 ± 600	0.736
	Continuous	2062 ± 481		58.6 ± 10.5		934 ± 214	

Table 5: Comparison of secondary (urine output, eGFR & BNP) outcomes among both study groups (stratification analysis)

Subgroup	Treatment	Urine Output (mL)	p-value	eGFR	p-value	BNP (pg/mL)	p-value
Male (n=32)	Intermittent	2558 ± 816	0.062	51.3 ± 28.2	0.175	904 ± 744	0.841
	Continuous	2105 ± 462		62.1 ± 13.4		943 ± 225	
Female (n=28)	Intermittent	2902 ± 837	0.002	56.5 ± 19.6	0.428	847 ± 380	0.676
	Continuous	2048 ± 405		61.1 ± 8.3		896 ± 203	
≤50 Years (n=37)	Intermittent	2712 ± 856	0.006	55.3 ± 29.2	0.572	767 ± 620	0.493
	Continuous	2066 ± 412		59.4 ± 10.8		874 ± 245	
>50 Years (n=23)	Intermittent	2729 ± 826	0.038	51.3 ± 15.1	0.018	1043 ± 535	0.812
	Continuous	2099 ± 480		65.5 ± 11.2		1003 ± 106	
BMI<25 kg/m^2 (n=23)	Intermittent	2898 ± 853	0.011	46.0 ± 26.0	0.109	917 ± 785	0.899
	Continuous	2080 ± 485		60.2 ± 10.6		885 ± 235	
BMI≥25 kg/m^2 (n=37)	Intermittent	2599 ± 816	0.018	58.8 ± 22.4	0.534	851 ± 448	0.429
	Continuous	2077 ± 409		62.5 ± 11.6		942 ± 203	
Duration of symptoms <24h (n=21)	Intermittent	2556 ± 1076	0.142	47.4 ± 19.0	0.006	741 ± 726	0.363
	Continuous	1987 ± 487		68.6 ± 10.8		959 ± 127	
Duration of symptoms ≥24h (n=39)	Intermittent	2813 ± 664	<0.001	57.3 ± 26.7	0.899	956 ± 507	0.671
	Continuous	2124 ± 404		58.2 ± 9.8		902 ± 246	
Hypertensive (n=32)	Intermittent	2519 ± 879	0.138	52.3 ± 30.7	0.252	940 ± 787	0.863
	Continuous	2170 ± 373		61.5 ± 11.5		906 ± 221	
Non-Hypertensive (n=28)	Intermittent	2894 ± 770	0.001	54.9 ± 18.0	0.247	823 ± 370	0.320
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Diabetic (n=24)	Intermittent	2373 ± 669	0.211	55.8 ± 14.9	0.096	871 ± 612	0.845
	Continuous	2096 ± 379		65.1 ± 11.2		906 ± 218	
Non- Diabetic (n=36)	Intermittent	2892 ± 863	0.002	52.6 ± 28.2	0.429	881 ± 600	0.736
	Continuous	2062 ± 481		58.6 ± 10.5		934 ± 214	

DISCUSSION

Our data reveal clear renal benefits associated with continuous infusion, as indicated by markedly reduced creatinine levels (1.33 vs 1.78 mg/dL, p=0.004) and BUN levels (18.32 vs 36.40 mg/dL, p<0.001). These findings support the mechanistic concept that continuous administration of furosemide ensures more consistent intravascular volume and renal perfusion than the haemodynamic variations caused by bolus dose.[ix] The renal advantages

were especially notable in high-risk subgroups: diabetics demonstrated a remarkable 21.9 mg/dL reduction in BUN (p=0.003), whereas older patients (>50 years) displayed considerable preservation of eGFR (65.5 vs 51.3 mL/min/1.73m², p=0.018). This aligns with recent KDIGO guidelines indicating that continuous infusion may alleviate the course of cardiorenal syndrome in at-risk people.[x] The intermittent group demonstrated a 30.8% increase in urine production (2718.90 vs 2078.18 mL, p<0.001), particularly pronounced in females (854 mL, p=0.002) and normal-weight patients (Δ818 mL, p=0.011). This may pertain to elevated peak furosemide concentrations resulting in enhanced natriuresis during bolus dosing.[xi] The diuretic benefit was evident even in late presenters (≥24h symptoms), indicating that intermittent dosage continues to be helpful despite possible diuretic resistance. Nonetheless, this resulted in worse kidney biomarkers, underscoring a significant trade-off that clinicians must evaluate.

Our stratification demonstrated clinically significant variances in response; such as females had a better diuretic response to bolus administration but shown reduced renal protection from infusion compared to males. This sexual dimorphism may be associated with observed variations in furosemide pharmacokinetics.[xii] Younger individuals experienced enhanced renal protection from infusion, but elderly patients exhibited a distinct improvement in eGFR. This corresponds with the concepts of geriatric pharmacology, wherein consistent medication administration prevents renal damage caused by hypotension.[xiii] The significant reduction in BUN among diabetics receiving infusion (p=0.003) indicates a specific advantage for this high-risk population, potentially via circumventing diuretic resistance generated by hyperglycemia.[xiv] In contrast, non-hypertensives exhibited a remarkable response to bolus dose (953 mL, p=0.001), likely attributable to maintained vascular compliance.

Our results corroborate and enhance the current literature on furosemide administration techniques in AHF. Several critical insights arise when situating our findings within the framework of previous studies. Such as, our demonstration of enhanced renal preservation through continuous infusion (reduced creatinine and BUN, $p < 0.01$) substantiates the findings of Zheng et al.,[xv] who indicated a significantly greater freedom from congestion (69.05% vs. 43.59%, $p = 0.02$) and improved dyspnoea scores in patients with renal impairment receiving continuous infusion. Our findings, however, diverge from the meta-analysis conducted by Kugasenanchettiar et al.,[xvi] which reported no significant difference in deteriorating renal function across the strategies (RR 1.12, 95% CI 0.86–1.48). This divergence may arise from our emphasis on particular high-risk populations (e.g., diabetics, elderly), indicating that the renal advantages of continuous infusion may be contingent upon the population.

Increased urine output with intermittent bolus dose (2718.90 vs. 2078.18 mL, $p < 0.001$) contradicts past studies,[5,xvii] that preferred continuous infusion for diuresis (mean difference 461.5 mL/24h, $p < 0.01$). Our subgroup study indicated that this benefit was predominantly influenced by females and non-hypertensives, a detail overlooked in previous aggregated research. The DOSE experiment likewise indicated no difference in mortality but emphasised the balance between diuresis and renal function, reflecting our results.[xviii]

The analogous BNP drop among groups ($p = 0.706$) corresponds with the findings of Palazzuoli et al.,[xix] who noted no disparity in mortality despite a more substantial BNP reduction with continuous infusion. Nonetheless, their six-month follow-up revealed elevated readmission rates associated with continuous infusion (58% vs. 23%, $p = 0.001$), highlighting the necessity for long-term research to reconcile short-term renal advantages with possible subsequent hazards. Our segmentation based on comorbidities and demographics rectifies deficiencies in prior research. The significant renal protection observed in diabetics receiving continuous infusion (BUN Δ21.9 mg/dL, $p = 0.003$) corroborates the findings of Jaya Shree et al,[xx] who reported deteriorating renal function with intermittent dosage. In contrast, the enhanced diuresis observed in females receiving bolus dose (Δ854 mL, $p = 0.002$) represents a novel discovery not previously emphasized.

Limitations:

Several limitations should be acknowledged while analysing the results of this investigation. This single-center study, undertaken at a single institution, may yield results that are not entirely applicable to other healthcare environments with varying patient demographics or clinical methodologies. The brief follow-up duration of 48-72 hours for outcome evaluation precludes any inferences regarding the long-term impacts on renal function, mortality, or hospital readmission rates, all of which are crucial in the management of heart failure. The open-label trial design increases the possibility of bias, since

physicians' management decisions may have been swayed by their awareness of the treatment assignment, notwithstanding our implementation of objective outcome measures.

The trial utilized a fixed weight-based furosemide dosing approach instead of individualised dose titration according to clinical response, which may not adequately represent real-world practices where dosing is often modified. Although our subgroup analyses yield vital first insights into varying treatment effects, certain subgroups (such as diabetic or elderly patients) have relatively small sample sizes, constraining our ability to identify potentially significant clinical differences. The lack of haemodynamic monitoring data, such as central venous pressure or cardiac output measurements, limits our capacity to comprehensively elucidate the processes behind the observed renal protection associated with continuous infusion. Ultimately, we did not consistently account for other potential confounding variables, including concomitant medications (such as ACE inhibitors or beta-blockers), hydration state, or dietary sodium intake, all of which may have impacted our results. These limitations underscore opportunities for enhancement in future study while provide context for the interpretation of our present findings.

CONCLUSIONS

Our study demonstrated that continuous furosemide infusion provides superior renal protection, while intermittent bolus dosing achieves greater diuresis in acute heart failure patients. The choice of regimen should be individualized based on patient characteristics, prioritizing renal safety in high-risk subgroups and aggressive fluid removal when rapid decongestion is needed. Personalized approaches may optimize outcomes in AHF management.

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