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ORIGINAL ARTICLE

Continuous Versus Intermittent Furosemide Dosing Regimen in the Treatment of Acute Decompensated Heart Failure

Hira Ahmad[1], Samiullah Khan[2], Saadullah Shah[3], Sunehra Iqbal[4], Muhammad Niaz Khan[5], Naveed Danish[6]

[1]*Cardiologist at Health Department Gilgit*
[2]*Associate Professor Cardiology, Bannu Medical College/DHQ-TH Bannu*
[3]*Assistant Professor Cardiology at Bannu Medical College/DHQ-TH Bannu*
[4]*Medical Officer with DHO, Bannu*
[5]*Fellow Interventional Cardiology, Hayatabad Medical Complex, Peshawar*
[6]*Consultant Cardiologist, DHQ Hospital, Nowshera*

Correspondence:
Dr. Samiullah khan
Associate Professor Cardiology, Bannu Medical College/ DHQ-TH
drsamee@yahoo.com

Abstract

Objective: To compare continuous versus intermittent (bolus) infusion of furosemide in patients with acute decompensated heart failure (ADHF) in terms of length of hospital stay, urine output per day and change in serum creatinine levels.
Duration: Six months (01-09-2021 to 28-02- 2022)
Setting: Cardiology department District Head Quarter Teaching Hospital (DHQ-TH) Bannu.
Methodology Eighty-two (n=82) adult patients of either gender, between age 50 years to 70 years were enrolled and equally divided into Group A (continuous Furosemide infusion) and group B (intermittent Furosemide dosing). Outcome of the therapy were duration of hospital stay, changes in serum creatinine and daily urine output.
Results: Mean length of hospital stay was significantly shorter (5.8±2.4 days versus 6.9±2.3, p=0.04), urine output per 24 hours was higher (2796.3 ml ± 365.9 SD and 2720.7 ml ± 647.6 SD, p=0.517) and mean change (rise) in serum creatinine was significantly higher (0.41 mg/dL ± 0.26 SD and 0.27 mg/dL ± 0.32 SD respectively, p=0.027) in continuous infusion group when compared with intermittent dosing group.
Conclusions: Treatment with continuous infusion of furosemide resulted in higher urine output per 24 hours, a higher rise in mean serum creatinine and a shorter duration of hospital stay as compared to treatment with intermittent dosing regimen.

KEY WORDS: Heart Failure, Acute decompensate heart failure, Diuretic therapy for ADHF
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Introduction

Heart failure (HF) is a life-threatening progressive disease characterized by signs and symptoms of fluid overload often caused by a structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures.[1] The main manifestations of the syndrome are symptoms resulting from vascular congestion, such as shortness of breath, abdominal distension, edema formation and symptoms resulting from low systemic perfusion.[2] Acute decompensated heart failure (ADHF) considered as the leading cause of hospital admissions in Europe and United states with over 1 million annual hospitalizations, accounting for 1-2% of all hospitalizations.[3,4,5] Rising stress of socio-economics issues in the modern era combine with greasy food and little exercise result towards increased prevalence of heart failure in Pakistan that is estimated to be 110 per million.[6] Removal of excess extracellular fluid with diuretics to treat peripheral and/or pulmonary edema is one of the mainstays of volume management.[7,8] Use of dieresis is

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often limited by their adverse effects on renal profile, electrolytes and hemodynamic consequences. [9,10] Their mode of administration is as either bolus doses or continuous infusion. In theory, intermittent boluses could lead to more unfavorable hemodynamic changes, be associated with a higher rate of diuretic resistance due to suboptimal drug levels in the renal tubules, and result in a rebound in sodium reabsorption. On the other hand, continuous administration should provide more constant delivery of diuretic into the tubule, potentially reducing this phenomenon.[11] Various studies compare bolus doses with continuous infusion of diuretics in ADHF management, but there is no consensus about the mode of administration of diuretic treatment in HF patients. In a recent study, Palazzuoli A et al found that at discharge, the mean change in serum creatinine was higher (+0.8 ± 0.4 versus -0.8 ± 0.3 mg/dl *P* <0.01) and length of hospital stay was longer in the continuous infusion group (14.3 ± 5 versus 11.5 ± 4 days, *P* <0.03). However, urine output per day was higher in continuous infusion group (2295 ± 775 VS 2090 ± 421 ml; *P* <0.002).[12]

Although diuretic therapy and its mode of delivery is a widely studied topic,[9-16] prospective randomized clinical trials are lacking in our local population. The present study has been designed to compare outcomes of continuous versus bolus infusion of furosemide in patients with ADHF. The study results will help the clinicians to understand which mode of administration results in better clinical outcomes.

Material and Method

This was a prospective, Random Sampling Method, open label randomized, parallel-group study comparing the effectiveness of continuous intravenous (cIV) with intermittent intravenous (iIV) infusion of furosemide in 82 patients with ADHF. The dose and duration of furosemide as well as concomitant medications to treat ADHF were determined by physician preference based on each patient clinical status.

The study was conducted at Cardiology Department District Head Quarter Teaching Hospital (DHQ-TH) Bannu from (01-09-2021 to 28-02- 2022). Sample size was calculated by using WHO sample size calculator (7.4b) taking Level of significance:5%, Power of the test:80%, Population standard deviation:4.5[16], Test value of population mean (LOS in continuous arm):14.3 [16], Anticipated population mean (LOS in intermittent arm):11.5 [16], The sample size calculated comes out to be n=82 patients (41 patients in each group)

INCLUSION CRITERIA

All diagnosed patients of acute decompensated heart failure as per operational definition

- Both genders
- Age 50-75years

EXCLUSION CRITERIA

- Patients having end stage renal disease (eGFR ≤15ml/min)
- Patients with history of hospital admission for ADHF during the last one month.
- Recent (within one month) history of exposure to nephrotoxic drugs and contrast agents
- Patients who received more than two IV doses of furosemide or any continuous infusion of furosemide one month before randomization
- Patients with a systolic blood pressure <90 mm Hg or with serum creatinine levels >4.0 mg/dL
- Patients having cardiomyopathies other than ischemic variety (including diabetic cardiomyopathy).
- Patients having a baseline LVEF < 30%

There is no significant difference in outcomes of continuous and intermittent infusion of furosemide in patients with acute decompensated heart failure.

***Acute Decompensated Heart Failure*:** It shall be diagnosed clinically based upon the presence of a constellation of symptoms and signs of heart failure.[13,14,15]

Patients with prior history of HF – When such patients present with breathlessness [NYHA classIII and IV] and evidence of fluid retention (ie, elevated jugular venous pressure [>9 cm H_2O] or evidence of pulmonary edema on chest x-ray or peripheral edema on physical examination). Presence of both (breathlessness and evidence of fluid retention) will be diagnostic of ADHF

Patients with no prior history of HF – When such patients present with new onset orthopnea and normal body temperature (98.6^{o}F), presence of one of the following findings will be diagnostic of ADHF

1. elevated JVP (>9 cm H_2O),

2. typical chest radiograph findings of pulmonary edema (marked cardiomegaly and extensive bilateral interstitial markings)

***Length of hospital stay*:** It was estimated as total number days from day of enrollment into the study to the day of discharge following furosemide therapy.

***Urine output per day*:** Urine output per day was quantified by collecting the total urine output and documenting its volume each day.

***Change in serum creatinine levels*:** It was calculated by taking the difference from baseline serum creatinine and at the time of completion of furosemide therapy and was measured in mg/dl.

Approval of the study was sought from the hospital ethics committee for conducting the study. Patients who were diagnosed cases of ADHF according to our operational definition and those fulfilling the inclusion criteria were enrolled from the CCU & ICU of District Head Quarter Teaching Hospital (DHQ-TH) Bannu during first 6 hours of hospital admission. Informed written consent was taken. History taking and physical examination was performed by the Cardiologist on duty. Baseline laboratory investigations were performed. Echocardiography and chest radiography was done done to assess pulmonary congestion. Patients were randomly divided into 2 groups i.e. continuous infusion group or intermittent group by lottery method. Patients were then given either of continuous or bolus infusion of furosemide throughout their hospital stay or upon clinical improvement as perescribed in operational definition. Along with furosemide therapy, patients were also received their standard usual treatment (ACE inhibitors or ARBs, digoxin, nitrates, aspirin, statins, and digoxin) if and when considered appropriate. Patient body weight, urine output, chest X-ray, blood complete picture, renal function tests, serum sodium and potassium and ECG were repeated on a daily basis. Clinical improvement was assessed by decrease or disappearance in signs of pulmonary congestion, S3 gallop, improvement in chest X-ray findings, or reduction in dyspnea and orthopnea. Furosemide therapy was discontinued if patient developed cardiogenic shock, a hypokalemia of less than 2.0 mEq/L or a new rise of serum creatinine 30% above the baseline during treatment. Outcome of the therapy in terms of duration of hospital stay, change in serum creatinine and daily urine output was assessed according to the operational definition. All the data collection was conducted by the researcher herself/himself to maintain data quality and compliance to the study protocol. All the gathered information were entered in the proforma.

Data was entered and analyzed on computer software SPSS version 19. Quantitative variables like age, BMI, duration of heart failure, LVEF, change in serum creatinine level, urine output per day and duration of hospital stay were measured as mean ± SD. Frequencies and percentages were calculated for qualitative variables like gender and cardiac disease. Study outcomes in both groups were compared by applying t-test and p-value ≤0.05 was considered significant. Effect modifiers like age, gender, BMI and LVEF were controlled by stratification. Post stratification t-test will be applied and P-value ≤0.05 was considered as significant.

Results

Eighty-two (n=82) adult patients of either gender age 50-75 years admitted to cardiology department with ADHF were enrolled in the study. Forty-one (n=41) subjects each were randomly assigned into Group A (continuous Furosemide infusion) and group B (intermittent Furosemide dosing). Age, gender, baseline LVEF, Mean duration of disease and mean serum creatinine at baseline described in table 0I.

TABLE 01: BASE LINE CHARACTERISTICS IN BOTH GROUPS

AGE GROUPS (YEARS)	CONTINUOUS INFUSION	INTERMITTENT DOSING
50-60	19 (46.3%)	20(48.8%)
61-75 YEARS	22 (53.7%)	21(51.2%)
GENDER		
MALES	19 (46.3%)	22 (53.7%)
FEMALES	22 (53.7%)	19 (46.3%)
BMI GROUPS		
<30 kg/m^2	20 (48.8%)	23 (56.1%)
≥30 kg/m^2	21(51.2%)	18 (43.9%)
BMI (kg/m^2) MEAN±SD	29.1±3.1	29.7±3.2
LVEF GROUPS		
30-39%	30 (73.2%)	24 (58.5%)
40-45%	11(26.8%)	17(41.5%)
LVEF (%) MEAN±SD	33.1±5.9	34.1±6.7
MEAN SERUM CREATININE BASELINE (mg/dl)	1.36 ±0.52	1.53± 0.69

LENGTH OF HOSPITAL STAY (MEAN DAYS)	5.8 ±2.4,	6.9 ±2.3

Mean length of hospital stay was 5.8±2.4 days in continuous and it was 6.9±2.3 days in intermittent infusion group (p=0.04, table 02). Mean length of hospital stay was significantly shorter in patients underwent continuous infusion when compared to those underwent intermittent infusion.

Table 02: Outcomes Of Therapy In Both Groups

PARAMETER	GROUP A	GROUP B	t-TEST
	CONTINUOUS	INTERMITTENT	P-VALUE
Hospital Stay (Days)	5.8 ±2.4	6.9±2.3	0.04
Urine Output 24 Hours (ml)	2796.3±365.9	2720.7 ±647.6	0.517
S. Creatinine Change(mg/dl)	0.41±0.26	0.27±0.32	0.027
Age Groups 50-60 yr	7.0±2.3	7.4 ±2.5	0.601

Urine output per 24 hours was higher in continuous infusion group when compared with intermittent dosing group (2796.3 ml ± 365.9 SD and 2720.7 ml ± 647.6 SD respectively). However, the difference was not statistically significant (p=0.517, table II).

Mean change (rise) in serum creatinine was higher in continuous infusion group when compared with intermittent dosing group (0.41 mg/dL ± 0.26 SD and 0.27 mg/dL ± 0.32 SD respectively). The difference was statistically significant (p=0.027, table III).

Similar trend (treatment with continuous infusion of furosemide resulted in higher urine output per 24 hours, a higher rise in mean serum creatinine and a shorter duration of hospital stay as compared to treatment with intermittent dosing regimen) was observed when outcomes were stratified for effect modifiers like age, gender, BMI Table III and baseline LVEF (Table IV).

TABLE IV: Outcomes Of Therapy In Both Groups (LVEF Stratification)

LVEF Groups	GROUP		Duration Of Hospital Stay (days)	URINE OUTPUT PER 24HOURS (ml)	Creatinine Change (mg/dl)
30-39%	continuous infusion	Mean	5.3	2773.3	0.41
		SD	2.6	400.8	0.26
	intermittent dosing	Mean	6.9	2564.6	0.25
		SD	1.7	645.1	0.28
	p-value t-test		**0.536**	**0.151**	**0.040**
40-45%	continuous infusion	Mean	4.6	2859.1	0.42
		SD	1.2	252.8	0.25
	intermittent dosing	Mean	8.4	2941.2	0.32
		SD	2.6	601.6	0.42
	p-value t-test		**0.001**	**0.673**	**0.439**

Table III: Outcomes Of Therapy In Both Groups By Age, Gender & BMI Stratification)

	Parameter	Hospital Stay (Days)	Urine Output 24Hr(ml)	Creatinine Change (mg/dl)
Age Group 50-60	Continuous	7.0±2.3 p <0.601	2855.3 ±464.8 P<**0.197**	0.41 ±0.29 P,**0.186**
	Intermittent	7.4 ±2.5, p <0.601	2657 ±474.1 P< **0.197**	0.28 ±0.27 P<**0.186**
Age Group 61-75	Continuous	4.9 ± 2.1 <**0.021**	2745.5 ±253.1 P<**0.841**	0.41 ±0.22 P<**0.085**
	Intermittent	6.5 ±2.3 <**0.021**	2780.9 ±785.7 P<**0.841**	0.25 ±0.37 P<**0.085**
Males Gender	Continuous	4.5 ±1.9 P<0.005	2818.4 ±2.5.6 P<0.020	0.43 ±0.22 P<0.068
	Intermittent	6.5 ±2.4 P<0.005	2450.1 ±633.4 P<0.020	0.29 ±0.39 P<0.068
Female Gender	Continuous	6.1 ±2.2 P< 0.617	2777.3 ±466.9 P<**0.104**	0.39 ±0.29 P<**0.226**
	Intermittent	7.4 ±2.4 P< 0.617	3.34.2 ±520.2 P< **0.104**	0.29 ±0.24 P<**0.226**
BMI <30 Kg/m^2	Continuous	5.1 ±2.3 P<**0.060**	2705.1 ±373.4 p<**0.355**	0.45 ±0.21 P<**0.003**
	Intermittent	6.3 ±2.1 P<**0.060**	2547.8 ±665.6 p<**0.355**	0.25 ±0.14 P<**0.003**
≥30 Kg/m^2	Continuous	1.6 ±2.3 1.7 P<0.194	2883.3 ±345.1 p <**0.696**	0.39 ±0.12 p<**0.690**
	Intermittent	7.7 ±2.6 P<0.194	2941.7 ±566.8 p <**0.696**	0.37 ±0.31, p<**0.690**

Discussion

A total of eighty-two (n=82) adult patients of either gender with between 50-75 were enrolled and equally divided into Group A (continuous Furosemide infusion) and group B (intermittent Furosemide dosing). Our results showed that Mean length of hospital stay was significantly shorter (5.8±2.4 days versus 6.9±2.3, p=0.04), urine output per 24 hours was higher (2796.3 ml ± 365.9 SD and 2720.7 ml ± 647.6 SD, p=0.517) and mean change (rise) in serum creatinine was significantly higher (0.41 mg/dL ± 0.26 SD and 0.27 mg/dL ± 0.32 SD respectively, p=0.027) in continuous infusion group when compared with intermittent dosing group.

We found larger volumes of diuresis with continuous infusion regimen but on the other hand, it was associated with greater elevations in serum creatinine. The findings suggest that the rate of salt and water loss was more than that of plasma refill from the extra vascular compartment. Our results are comparable with already reported studies on the subject**.** Malkiwodeyar PK, [16] in their study on acute decompensated HF subjects during hospitalization demonstrated greater urine output and greater reduction in BNP with continuous infusion in comparison with intermittent infusion. They also reported that continuous infusion of loop diuretics was associated with higher rates of acute kidney injury.[78] Another study (the ESCAPE trial) reported the similar observations.[17]

Our results are also in accordance with the DOSE trial that randomized more than 300 subjects with ADHF to high/low dose and continuous/intermittent furosemide infusion. They did not find superiority in either the dose (high/low) or administration (infusion/bolus) arms.[18]

It is assumed that continuous infusion of diuretics provides a more constant urine output, results in less variations of intravascular volume and less reabsorption of sodium. This is likely because continuous administration results in higher concentration of drug at the loop of Henle. This higher drug concentration reduces the energy requirement of the cells at medullary level and hence provides protection during state of hypoxia. However, these benefits of continuous administration should be evaluated against constant neuroendocrine activation, greater counter-regulatory attempts to increase reabsorption of water and sodium and sustained vasoconstriction of efferent arterioles.[19,20] A systematic review demonstrated that with continuous infusion of diuretics ultimate results are lower urine outputs and greater rates of side effects.[12]

Greater degree of diuresis with the use of continuous infusion of loop diuretics has also been reported by Palazzuoli A, et al. Nonetheless, it was associated with greater rise in serum creatinine levels, use of additional treatment, higher rates of hospital admissions and mortality within 6 months.[7] Thomson MR, reported similar findings in their study. They found that the continuous infusion of furosemide provided more efficient dieresis, was well tolerated and significantly more effective than intermittent dosing regimen. However, in contrast to the present study, they did not find any significant difference in safety measures between the groups.[11]

Study limitations: In the present study, BNP, urinary sodium were not estimated, which could be helpful in accurately determining the cause of greater elevations in serum creatinine with continuous infusion. Secondly, we did not measure long-term outcomes like rate of re hospitalizations and mortality.

Conclusion

Treatment with continuous infusion of furosemide results in higher urine output per 24 hours, a higher rise in mean serum creatinine and a shorter duration of hospital stay as compared to treatment with intermittent dosing regimen.

We suggest that the lowest possible dose of diuretics should be administered initially to preserve renal function while treating patients with ADHF.

We further suggest that different modes of administration with physiological tailoring of dose of diuretics may be the areas for future research.

Conflict of Interest: No
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