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Continuous Versus Bolus Dosing of Furosemide in the Treatment of Patients with Acute Decompensated Heart Failure

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Abstract: In cases of acute decompensated heart failure, Loop diuretics are important modality of treatment, but there are few study to guide there use. Patients admitted with ADHF were randomized into two groups - continuous infusion and bolus therapy group with furosemide. Following are considered as the end points, negative fluid balance, duration of hospital stay, trend of serum electrolytes and one month clinical outcome (Death and hospital readmission).Total 50 patients were included in the study (25 in each group). We noticed that there was significant diuresis in the first 24 hour and shorter hospital stay in bolus group. There was no significant difference in serum sodium and potassium levels and hospital readmission. There was no significant difference in the renal parameters. Both continuous infusion and bolus dose diuretic modality of treatment have equal role in the management of ADHF with no significant difference in the renal function and electrolytes level. Bolus dose diuretic strategy has been associated with shorter hospital stay and rapid improvement in clinical symptoms so, it might be effective diuretic strategy.
Keywords: Heart failure, diuretics, bolus, infusion, furosemide

INTRODUCTION

Loop diuretics are the important modality of treatment in patients with Acute Decompensated heart failure [1]. Though diuretics form an important modality of treatment, there are very sparse studies regarding the guidance of the therapy and most of present guidelines depend on the opinion of experts [2, 3].

Loop diuretics have their effect on renal parameters, serum electrolytes, splanchnic blood flow and drugs metabolism so there will be variable response in ADHF [4-6]. We sought to determine if there are any differences in clinical outcomes between intravenous bolus and continuous infusion of loop diuretics.

AIM

To study the various diuretic strategies in patients with ADHF and its impact on the course of heart failure patients, including the morbidity and mortality.

MATERIAL AND METHODS

This study was conducted from March 2016 to March 2017 at the intensive care unit KIMS Hubli.

Inclusion criteria

HF was defined by at least one symptom (dyspnea, orthopnea, or edema) and one sign (rales on auscultation, peripheral edema, and ascites) or pulmonary vascular congestion on chest radiography.

- Patients age more than ≥18 years old admitted with heart failure.
- Patients with prior clinical diagnosis of heart failure (HF) on daily home use of oral loop diuretic for at least one month.
- Patient identified within 18 h of hospital admission.
- Patients willing to give consent for the study.

Exclusion criteria

- Patient in shock defined by Systolic BP< 80 mmHg.
- Patient with significant renal dysfunction defined by Serum creatinine >3.50 mg/dl at baseline or need of renal replacement therapy.
- Patient who underwent recent contrast study.

Study design

This was a prospective, randomized, double-blind study comparing bolus dose versus continuous infusion dose of furosemide in patients of ADHF. Patients who were diagnosed with ADHF were initially given 40 mg of furosemide then they were randomized into two groups - intravenous furosemide bolus 100 mg/24 h in two divided doses and intravenous furosemide continuous infusion 100 mg/24 h (Intravenous furosemide 100 mg = 10 ml was dissolved in 14 ml of 0.9% normal saline to form a solution of 24 ml. This was given at the rate of 1 ml/h infusion or was given in two divided bolus doses depending upon the treatment group). A written and informed consent for study treatment and data collection was obtained from each patient. At the time of admission patient's clinical symptoms and signs of heart fail were noted – paroxysmal nocturnal dyspnea, orthopnea, pedal edema, ascitis, blood pressure, and jugular venous pressure were noted. Patient's baseline clinical data and previous drugs intake listed. We evaluated the electrocardiogram, left ventricular ejection fraction, serial renal parameters. We assessed urine output at 24 hour at bedside and weight loss, length of hospital stay, serial serum electrolytes and renal parameters were noted. We also assessed two months clinical outcome (death and emergency department visits).

STATISTICAL ANALYSIS

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables.

Paired t test is the test of significance for paired data such as before and after surgery for quantitative data. Statistical significance was assessed using p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS

Overall 50 patients were enrolled in the study. The baseline clinical data are summarized in Table -1. Majority of the patients were males (68.0%). Most of them had high risk features such as hypertension (82%), diabetes (62%) and prior history of CAD (68%). Dyspnea and orthopnea were the most common presentation (82%), pedal edema (68%) The mean Left ventricular ejection fraction (LVEF) was 33.3%. There was no statistically significant difference between the two groups of patients regarding demographics, risk factors and symptoms. In the study mean duration of hospital stay in bolus group was 8.8 ± 1.8 days and in continuous group was 12.8 ± 2.6 days. This difference in duration of hospital stay was statistically significant. In the study there was no significant difference in serum sodium and potassium levels between two groups; significant difference was observed in mean potassium levels between two groups. In this study we noticed that 36% of bolus group and 48% of continuous group required readmission during follow up.

Table-1: The demographic profile of the patients in two groups.

	Total		Bolus		Infusion		P value
	Count	%	Count	%	Count	%	
Age (years) Mean ± SD	55.9 ± 10.2		57.08 ± 9.87		54.6 ± 10.4		0.401
Male	34	68%	17	50%	17	50%	1.000
Diabetes	31	62%	18	72%	13	52%	0.145
Hypertension	41	82%	21	84%	20	80%	0.713
Dyspnea or Orthopnea Day1	41	82%	21	84%	20	80%	0.713
Edema	34	68%	21	84%	13	52%	0.015*
Rales	31	62%	14	56%	17	68%	0.382
JVP	35	70%	18	72%	17	68%	0.758
Antiplatelet	11	22%	4	16%	7	28%	0.306
Angiotensin converting enzyme inhibitors	34	68%	18	72%	16	64%	0.544
Beta blockers	26	52%	14	56%	12	48%	0.571
Spironolactone	20	40%	9	36%	11	44%	0.564
Pulse (beats per minute)	111.2 ± 10.4		109.6 ± 8.8		112.8 ± 11.8		0.289
Systolic BP (mmHg)	151.1 ± 9.7		153.2 ± 9.6		149.0 ± 9.5		0.131
Diastolic BP (mmHg)	90.1 ± 5.4		90.4 ± 6		89.8 ± 4.9		0.640

Table-2: Blood Urea Comparison between two groups at different time periods of follow-up

Blood Urea	Group				P value
	Bolus		Continuous Infusion		
	Mean	SD	Mean	SD	
1st day	41.0	4.1	40.9	4.1	0.918
3rd day	43.2	2.1	42.7	2.8	0.492
7th day	44.8	1.6	44.3	2.2	0.348
30th day	44.6	1.4	44.2	2.5	0.447

Table-2: shows that, in the study Mean Blood Urea were higher in Bolus group compared to Continuous infusion at all the intervals of follow-up. This difference in Mean blood urea was not statistically significant.

Table- 3: Serum Creatinine Comparison between two groups at different time periods of follow-up

Serum Creatinine	Group				P value
	Bolus		Continuous Infusion		
	Mean	SD	Mean	SD	
1st day	1.44	0.20	1.56	0.27	0.066
3rd day	1.31	0.20	1.34	0.29	0.628
7th day	1.27	0.22	1.27	0.28	0.995
30th day	1.31	0.25	1.23	0.15	0.157

Table- 3: shows that, in the study Mean Serum Creatinine there was no significant difference between two groups at all the intervals.

Table-4: Serum Sodium Comparison between two groups at different time periods of follow-up

Serum Sodium	Group				P value
	Bolus		Continuous Infusion		
	Mean	SD	Mean	SD	
1st day	134.48	2.97	135.36	3.58	0.182
3rd day	132.36	3.89	133.36	2.43	0.281
7th day	131.68	3.63	132.12	1.17	0.567
30th day	133.00	4.58	133.36	1.60	0.712

Table 4 shows, in the study there was no significant difference in mean Serum Sodium between two groups at all the intervals.

Table -5: Serum Potassium Comparison between two groups at different time periods of follow-up

Serum Potassium	Group				P value
	Bolus		Continuous Infusion		
	Mean	SD	Mean	SD	
1st day	4.02	0.31	4.10	0.31	0.343
3rd day	3.50	0.27	3.64	0.45	0.194
7th day	4.15	0.40	3.98	0.30	0.113
30th day	4.25	0.32	4.15	0.27	0.257

Table 5: shows in the study there was no significant difference in mean Serum potassium between two groups at all the intervals.

Table-6: Urine output comparison between two groups at different time periods of follow-up

Urine Output	Group				P value
	Bolus		Continuous Infusion		
	Mean	SD	Mean	SD	
Till 24 hr	1133.58	142.05	755.28	42.66	<0.001*
24 to 48 hr	720.32	141.10	887.44	43.94	<0.001*
48 to 72 hour	712.84	128.52	909.76	51.24	<0.001*

Table 6: shows comparison of fluid loss at various intervals between the two groups. There was stastistical difference in urine output at 0-24 hour; urine output was more in bolus group during first 24 hour of hospital admission as compared to the continuous infusion group. Between 24 to 48 hour and 48 to 72 hour, urine output in the continuous infusion group was 887.44 and 909.76 successively as compared to the 720.32 and 712.84 successively in the bolus group the difference was statistically significant.

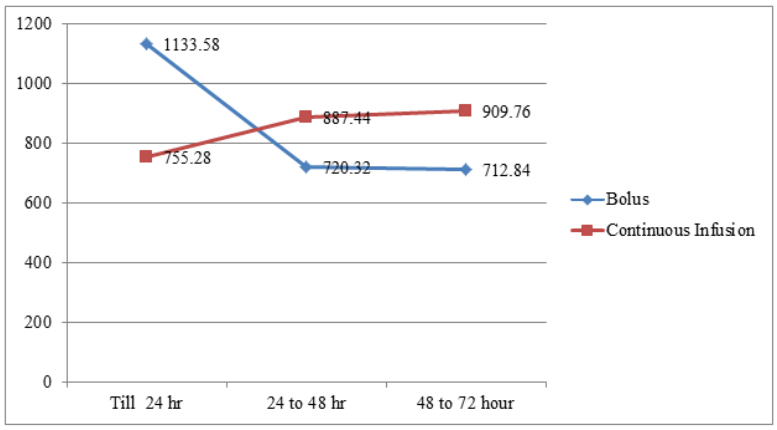

Fig-1: Diagram showing Urine output comparison between two groups at different time periods of follow-up

DISCUSSION

ADHF associated with pulmonary congestion and volume overload with high morbidity and mortality. Loop diuretics are an essential component of therapy for acute decompensated heart failure; there have been few prospective data to guide decision-making regarding the use of these agents.

In our study we noted that there was more diuresis in the first 24 h, hospital stay was short with the bolus dose, there was no difference in renal function, serum sodium or serum potassium levels between the groups and no difference in the number of emergency department visits at one month among the three groups.

There was a more loss of fluid in the bolus group between 0–24 h as compared to infusion group. This could be because of a faster initial diuresis in bolus group. The bolus-dose strategy was, associated with greater relief of dyspnea, greater fluid loss and weight loss [6].

A pooled analysis of prospective randomized controlled studies prior to 2004 concluded that continuous infusion was beneficial in terms of increased urine output and a better safety profile.[7] However, the studies included in the analysis were quite small (254 patients in total) and heterogeneous in design, and the advantage disappeared when two studies using hypertonic saline were excluded.

Recent studies have failed to reach a consensus. Allen *et al.* [8] found no advantage with continuous infusion, whereas A Meta-analysis by Salvador *et al.*[7] (95%CI 93.1 to 449; $p < 0.01$), and studies by Thomson *et al.* [9], Pivac *et al.*[10] and Dormans *et al.* [11] showed greater diuresis with continuous infusion than bolus group, but studies by Aaser et al [12] and Schuller *et al.* [13] found no difference between the diuretic effects of the two study groups.

There is limited evidence to guide diuretic use, as reflected in practice guidelines. In DOSE trial[14], they compared bolus versus infusion and high dose versus low dose of furosemide. There was no difference in the net fluid loss at 72 h in bolus versus continuous infusion arms ($p = 0.89$).

We noted that in our study, there was shorter hospital stay in the bolus group. This could be because of rapid initial diuresis, so patient gets relief from the congestion and overload status early and so there was shorter hospital stay. However, other studies showed different results. In DAD-HF trial [15] length of

hospital stay were similar in the two groups (mean 5.3 versus 6.1 days; $p = 0.2$). In DOSE trial [14] the length of hospital stay was similar in bolus and infusion group (mean of 5 days; $p = 0.97$). Studies by Thomson *et al.* [9] and Patricia *et al.* [16] showed a shorter hospital stay with continuous infusion.

We noted that in our study there was no statistically significant difference in serum sodium, serum potassium, blood urea and serum creatinine levels at various time intervals between the two groups. In DOSE trial, there was no significant difference in serum creatinine levels from baseline to 72 h between bolus and infusion group ($p = 0.45$) [14]. In DAD-HF trial, the laboratory values at 24 h between the two groups were - serum sodium (mEq/l) (138 ± 4, 138 ± 4; $p = 0.593$), serum potassium (mEq/l) (3.9 ± 0.4, 4.2 ± 0.5; $p = 0.027$), urea (mg/dl) (62.5 ± 23.4, 58.9 ± 16.7; $p = 0.927$) and serum creatinine (mg/dl) (1.38 ± 0.52, 1.25 ± 0.33; $p = 0.679$). This difference in serum potassium level could be because of the difference in study design [15].

The number of emergency visits to the hospital for recurrent HF within the first month of discharge was not significant among the two groups. We had one death in the bolus and one in the infusion group during the one month follow up.

Limitations

- This was a single center study with a small sample size.
- We considered blood urea and serum creatinine as a measure to see for worsening renal function. Patient baseline weight and eGFR could not be determined as patients were clinically unstable.
- We did not consider other end points like relief of dyspnea and weight loss. We considered negative fluid balance as a measure of clinical benefit.

CONCLUSION

Both continuous infusion and bolus dose diuretic modality of treatment have equal role in the management of ADHF with no significant difference in the renal function and electrolytes level. Bolus dose diuretic strategy has been associated with shorter hospital stay and rapid improvement in clinical symptoms so, it might be effective diuretic strategy.

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