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Original Article

A prospective, randomized study to evaluate the efficacy of various diuretic strategies in acute decompensated heart failure

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ABSTRACT

Aim: To evaluate the safety and efficacy of various initial strategies of loop diuretic administration in patients with acute decompensated heart failure (ADHF) on diuresis, renal function, electrolyte balance and clinical outcomes.

Methods: Consecutive patients admitted with ADHF were randomized into three groups - intravenous furosemide infusion + intravenous dopamine, intravenous furosemide bolus in two divided doses and intravenous furosemide continuous infusion alone. At 48 h, the treating physician could adjust the diuretic strategy. Primary endpoint was negative fluid balance at 24 h after admission. Secondary end points were duration of hospital stay, negative fluid balance at 48, 72, 96 h, the trend of serum electrolytes, and renal function and 30 day clinical outcome (death and emergency department visits).

Results: Overall ninety patients (thirty in each group) were included in the study. There was a greater diuresis in first 24 h ($p = 0.002$) and a shorter hospital stay ($p = 0.023$) with the bolus group. There was no significant difference in renal function and serum sodium and serum potassium levels. There was no difference in the number of emergency department visits among the three groups.

Conclusion: All three modes of diuretic therapies can be practiced with no difference in worsening of renal function and electrolyte levels. Bolus dose administration with

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its rapid volume loss and shorter hospital stay might be a more effective diuretic strategy.

1. Introduction

Acute decompensated heart failure (ADHF) is a common cause for admission to intensive care units. Most of these patients are treated with intravenous diuretics.[1] Though diuretics are the mainstay of treatment from many years, there are very few randomized and prospective trials to guide therapy and most of the guidelines are formulated upon opinion of experts.[2,3] Not all patients with heart failure respond equally to diuretics. The response is altered by renal impairment, drug interactions, variations in splanchnic flow and drug metabolism.[4–8] Though different protocols of diuretic therapy have been tried; there is no definite consensus as to which therapy is preferable. Hence, we conducted a prospective, randomized study to evaluate the efficacy of various diuretic strategies in acute decompensated heart failure.

2. Aim

To evaluate the safety and efficacy of various initial strategies of loop diuretic administration in patients with ADHF; on diuresis, renal function, electrolyte balance and clinical outcomes.

3. Material and method

This study was conducted from April 2010 to June 2012 at the intensive cardiac care unit of Madras Medical Mission Hospital, Chennai, India.

3.1. *Inclusion criteria*

- ≥18 years old
- 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 24 h of hospital admission
- HF was defined by at least one symptom (dyspnea, orthopnea, or edema) and one sign (rales on auscultation, peripheral edema, ascitis) or pulmonary vascular congestion on chest radiography
- Anticipated need for intravenous loop diuretics for at least 48 h
- Willingness to provide informed consent
- May be planned for intravenous dopamine (Dopa) infusion for heart failure.

3.2. *Exclusion criteria*

- Systolic BP <90 mmHg
- Serum creatinine >3.0 mg/dl at baseline or renal replacement therapy
- Patient planned for a procedure requiring intravenous contrast dye during the present admission.

Patient selection and treatment protocol – We prospectively enrolled consecutive patients with ADHF admitted to the emergency department of Madras Medical Mission, Chennai. They were administered a bolus of intravenous furosemide 40 mg. Then they were randomized into three

Table 1 – The demographic data of the patients in the three groups.

	Total	Infusion + Dopa ($n = 30$)	Bolus ($n = 30$)	Infusion ($n = 30$)	P value
Age (years)	58.22 ± 15.45[a]	56.07 ± 16.6	59.27 ± 16.46	59.32 ± 13.41	0.653
Male	66 (73.3%)	20/(66.7%)	23/(76.7%)	23/(76.7%)	0.6
Diabetes	49 (54.4%)	14/(46.7%)	18/(60.0%)	17/(56.7%)	0.559
Hypertension	53 (59%)	20/(66.7%)	17/(56.7%)	16/(53.3%)	0.553
Coronary Artery Disease	35 (39%)	12/(40.0%)	10/(33.3%)	13/(43.3%)	0.719
Smoker	16 (17.8%)	4/(13.3%)	6/(20.05%)	6/(20.0%)	0.738
Alcoholic	7 (7.8%)	4/(13.3%)	1/(3.3%)	2/(6.7%)	0.338
Dyspnea	80 (88.9%)	26/(86.7%)	25/(83.3%)	29/(96.7%)	0.232
Paroxysmal nocturnal dyspnea and orthopnea	53 (58.9%)	16/(53.3%)	17/(56.7%)	20/(66.7%)	0.551
Edema	35 (38.9%)	12/(40.0%)	13/(43.3%)	10/(33.3%)	0.721
Ascitis	7 (7.8%)	2/(6.7%)	3/(10.0%)	2/(6.7%)	0.856
Antiplatelets	68 (75.6%)	22/(73.3%)	23/(76.7%)	23/(76.7%)	0.942
Statin	55 (61.1%)	16/(53.3%)	17/(56.7%)	20/(66.7%)	0.551
Angiotensin converting enzyme inhibitors	35 (38.9%)	10/(33.3%)	13/(43.3%)	12/(40.0%)	0.721
Angiotensin receptor blockers	7 (7.8%)	0/(0.0%)	2/(6.7%)	5/(16.7%)	0.053
Beta blockers	39 (43.3%)	16/(53.3%)	14/(46.7%)	9/(30.0%)	0.171
Spironolactone	16 (17.8%)	6/(20.0%)	6/(20.0%)	4/(13.3%)	0.738
Pulse (beats per minute)	93.88 ± 27.18[a]	96.33 ± 36.60	92.93 ± 17.83	92.40 ± 24.51	0.793
Systolic BP (mmHg)	126.08 ± 27.21[a]	114.53 ± 20.03	130.80 ± 28.81	131.60 ± 28.47	0.01
Diastolic BP (mmHg)	77.77 ± 16.25[a]	69.53 ± 8.31	80.37 ± 15.08	84.77 ± 21.41	0.001

[a] Mean ± 2SD (standard deviation), Dopa = dopamine.

Table 2 – Comparison of input output (I/O) fluid loss (ml) at various intervals between infusion + Dopa, bolus and infusion groups.

I/O fluid loss at-	Infusion + Dopa				Bolus				Infusion				Kruskal–Wallis test applied		
	Mean	SD	Median	IQR[a]	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Chi-square	*p*-value	Difference is-
0–24 h	−612.34	349.58	−481.10	575.00	−1117.15	726.70	−828.00	733.75	−721.57	447.99	−628.00	390.50	12.508	0.002	**Significant**
24–48 h	−702.27	301.16	−825.00	477.00	−752.93	421.62	−751.00	547.00	−988.67	1143.49	−635.00	440.00	0.011	0.995	Not significant
48–72 h	−861.40	397.23	−825.00	692.00	−757.67	500.25	−544.00	580.25	−951.70	720.35	−745.00	713.25	2.278	0.320	Not significant
72–96 h	−763.23	357.09	−645.00	624.25	−688.56	218.72	−755.00	310.00	−722.52	299.00	−800.00	360.50	0.044	0.978	Not significant

[a] IQR = interquartile range.

groups, intravenous furosemide infusion 100 mg/24 h + intravenous dopamine 2.5 μg/kg/min, 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). At 48 h, the treating physician could adjust the diuretic strategy on the basis of patients' clinical response. The study protocol was approved by the institutional ethics committee. A written and informed consent for study treatment and data collection was obtained from each patient.

Data collection technique and tools – Patients' baseline characteristics on admission like diabetes, hypertension, smoking and alcoholism, history of coronary artery disease (CAD) and history of HF hospitalization in the past were collected. Patients' drugs which were used by him/her at home were noted on admission (especially the home dose of furosemide used by the patient for more than 1 month). All previous medications of the patient were continued. On arrival, patients' clinical symptoms and signs of HF - dyspnea, paroxysmal nocturnal dyspnea (PND), orthopnea, pedal edema, ascitis, pulse, blood pressure (BP) and jugular venous pressure (JVP) were collected. We evaluated the oxygen saturation (SpO_2), electrocardiogram (ECG), pulmonary congestion on chest X-ray and left ventricular ejection fraction (LVEF). Serial renal parameters and electrolytes were also assessed. All patients were encouraged to pass urine in a bedside calibrated can and those who were not able to do so underwent Foleys catheterization. The difference of total fluid intake and urine output was calculated at pre specified time intervals. Primary endpoint was negative fluid balance in each of these three groups at 24 h after admission. Secondary end points were duration of hospital stay, negative fluid balance at 48, 72, 96 h and the trend of serum sodium, serum potassium, blood urea, serum creatinine in the three groups at 24, 48, 72 h, 7 days and 30 days, in hospital and 30 day clinical outcomes (death and emergency department visits).

Data analysis – Data were collected prospectively. SPSS version 15.0 (SPSS Inc, Chicago, Illinois, USA) software was used for analysis. Continuous variables were summarized as mean ± standard deviation (SD) and categorical variables as percentages. Chi-square test, Fischer's Exact test were used. As data failed 'Normality' test, Kruskal–Wallis One Way Analysis of Variance on Ranks, Friedman Repeated Measures ANOVA, Wilcoxon Signed Rank test applied. All pair wise multiple comparison procedures were done by Tukey Test. Multiple Comparisons versus control group was done by Dunnett's method and Holm–Sidak method. These tests were applied with the help of a statistician. A p-value <0.05 was considered statistically significant.

3.3. *Results*

Overall 93 patients were enrolled in the study. One patient each expired in the infusion + dopamine group and bolus group during first 24 h of index hospitalization and one patient in infusion group got discharged against medical advice within 24 h of admission. These three patients were excluded

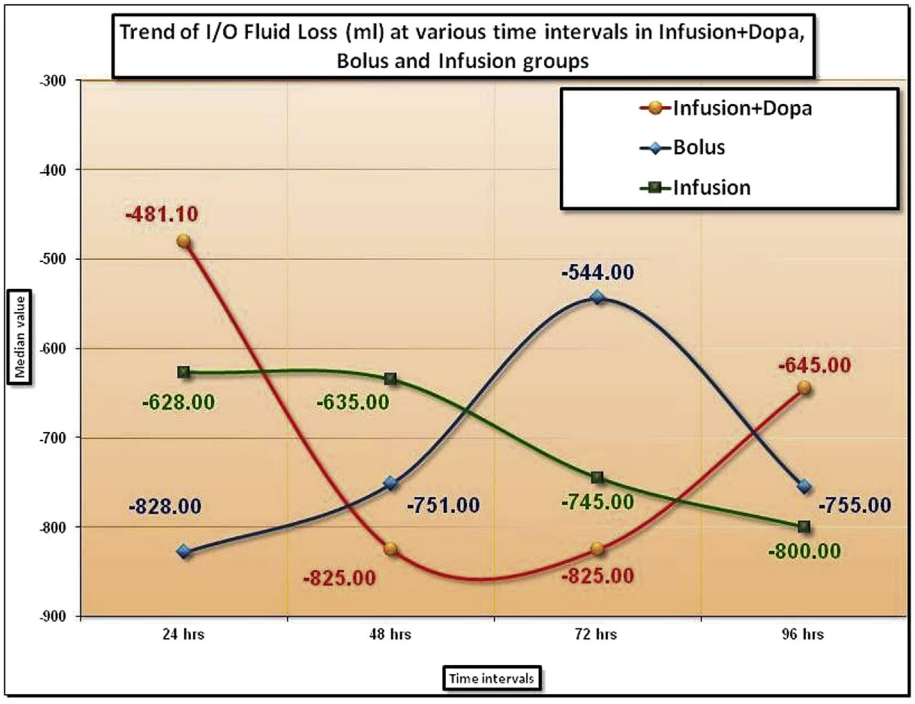

Fig. 1 – I/O fluid loss at various time intervals in infusion + Dopa, bolus and infusion groups.

from analysis. The baseline clinical data are summarized in Table 1. Majority of the patients were males (73.3%). Most of them had high risk features such as hypertension (59%), diabetes (54.4%), prior history of CAD (39%), and a prior history of hospitalization for HF (62.2%). Dyspnea was the most common presentation (88.9%), followed by PND and orthopnea (58.9%), pedal edema (38.9%), and ascitis (7.8%). The mean LVEF was 33%. There was no statistically significant difference between the three groups of patients regarding demographics, risk factors and symptoms. Admission BP was 114.53/69.53 ± 20.03/8.31 mmHg in the infusion + dopamine group, 130.80/80.37 ± 28.81/15.08 mmHg in the bolus group and 131.60/84.77 ± 28.47/21.41 mmHg in the infusion group. The difference was statistically significant [systolic BP ($p = 0.01$); diastolic BP ($p = 0.001$)]. The difference between home dose and dose after 48 h was statistically significant in all the three groups (infusion + dopamine – $p = 0.0066$, bolus – $p = 0.00134$, infusion – $p = 0.00007$).

Table 2 shows the comparison of fluid loss at various intervals between the three groups. The negative fluid balance was statistically significant between the three groups at 0–24 h ($p = 0.002$), but not statistically significant at other time intervals. Then we did pair wise comparison of fluid loss at 0–24 h between the three groups. This showed that the difference was statistically significant between infusion + dopamine versus bolus ($p < 0.05$), but not between infusion + dopamine versus infusion or bolus versus infusion groups. Then we statistically compared the amount of fluid loss at 0–24 h in each of the groups to the fluid loss at 24–48, 48–72, 72–96 h. The fluid loss in ml in the bolus group at 0–24, 24–48, 48–72, 72–96 h was [mean ± 2SD (median) – 1117.15 ± 726.70 (828); 752.93 ± 421.62 (751); 757.67 ± 500.25 (544); 688.56 ± 218.72 (755)] and the difference was significant ($p = 0.044$). The fluid loss in ml in infusion + dopamine group was 612.34 ± 349.58 (481.10); 702.27 ± 301.16 (825); 861.40 ± 397.23 (825); 763.23 ± 357.09 (645) and the difference was significant ($p < 0.001$). The fluid loss in ml in infusion group was 721.57 ± 447.99 (628); 988.67 ± 1143.49 (635); 951.70 ± 720.35 (745); 722.52 ± 299 (800) and the difference was not significant ($p = 0.692$). Fig. 1 shows the trend of loss of fluid in each group at various intervals.

The duration of hospital stay was 6.27 ± 3.43 days in infusion + dopamine group, 5.03 ± 3.33 days in bolus group and 6.77 ± 3.21 days in infusion group and the difference was statistically significant ($p = 0.023$). Pair wise comparison showed that the difference was significant between the bolus and infusion group ($p < 0.05$), but not significant between the bolus and infusion + dopamine or infusion and infusion + dopamine groups.

Tables 3–6 shows the comparison of serum sodium, serum potassium, blood urea and serum creatinine respectively. There was no statistically significant difference for the above mentioned parameters at various time intervals between the three groups ($p > 0.05$).

The number of emergency visits to the hospital for recurrent heart failure within the first month of discharge was 9 patients in infusion + dopamine, 8 in bolus and 7 in infusion groups ($p = 0.673$). We had two deaths in the bolus group and one in the infusion group during the 1 month follow up.

4. Discussion

The main findings of our study were: (1) greater diuresis in the first 24 h and shorter hospital stay with the bolus dose, (2) no difference in renal function, serum sodium or serum

Table 3 – Comparison of serum (S). Sodium (mEq/l) at various intervals between infusion + Dopa, bolus and infusion groups.

S. Sodium at-	Infusion + Dopa				Bolus				Infusion				One-way ANOVA applied		
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	*F*-value	*p*-value	Difference is-
Baseline	133.87	3.86	134.00	5.00	133.13	7.65	135.50	10.75	131.20	8.31	132.50	5.50	1.310	0.519	Not Significant (NS)
24 h	133.40	4.41	135.00	7.00	132.10	7.00	135.00	6.50	131.20	8.76	133.00	8.00	0.174	0.917	NS
48 h	133.53	4.64	133.00	5.00	131.30	5.69	132.50	5.25	131.77	6.45	135.00	6.00	2.071	0.355	NS
72 h	132.53	4.13	132.00	5.00	131.73	5.40	133.00	5.25	131.80	4.76	133.50	5.75	0.116	0.943	NS
7 days	131.67	4.57	130.00	5.00	131.57	4.33	132.50	4.00	131.13	4.07	131.00	6.00	0.389	0.823	NS
30 days	133.33	4.45	134.00	6.00	132.63	4.62	134.00	5.50	131.73	3.85	130.00	6.00	1.034	0.360	NS

Table 4 – Comparison of serum (S). Potassium (mEq/l) at various intervals between infusion + Dopa, bolus and infusion groups.

S. Potassium at-	Infusion + Dopa				Bolus				Infusion				One-way ANOVA applied		
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	*F*-value	*p*-value	Difference is-
Baseline	4.28	0.80	4.30	1.00	4.12	0.76	4.00	0.98	4.35	0.93	4.20	1.10	0.599	0.551	NS
24 h	3.99	0.73	3.90	1.00	3.89	0.51	3.90	0.95	4.22	0.95	4.10	1.43	1.576	0.213	NS
48 h	3.86	0.62	3.80	0.60	3.82	0.54	3.90	0.87	4.00	0.70	3.90	0.85	0.434	0.805	NS
72 h	3.86	0.51	3.90	0.50	3.80	0.54	3.80	0.52	4.09	0.55	3.90	0.80	2.480	0.090	NS
7 days	4.11	0.55	4.00	1.00	3.85	0.49	3.90	0.60	4.04	0.52	3.95	0.90	1.928	0.152	NS
30 days	4.19	0.42	4.20	0.60	4.01	0.50	4.00	0.40	4.01	0.39	4.00	0.53	4.968	0.083	NS

Table 5 – Comparison of Blood Urea (mg/dl) at various intervals between infusion + Dopa, bolus and infusion groups.

Blood urea at-	Infusion + Dopa				Bolus				Infusion				Kruskal–Wallis test applied		
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Chi-square	*p*-value	Difference is-
Baseline	44.73	21.77	39.00	35.00	43.67	18.59	39.00	26.25	51.23	29.94	36.00	45.25	0.183	0.912	NS
24 h	45.87	23.03	40.00	51.00	46.60	19.99	41.00	15.00	53.53	30.97	35.00	42.00	0.494	0.781	NS
48 h	49.80	31.16	41.00	55.00	51.77	26.03	43.00	33.00	52.37	32.03	37.00	35.00	0.666	0.717	NS
72 h	49.93	26.71	46.00	25.00	55.07	27.66	49.50	36.50	51.73	32.76	35.00	31.25	1.443	0.486	NS
7 days	51.27	27.14	45.00	31.00	54.60	25.82	46.00	32.75	45.93	24.47	33.00	38.00	3.407	0.182	NS
30 days	40.67	22.09	33.00	28.00	47.80	20.41	40.00	34.25	40.30	20.16	32.00	13.75	5.293	0.071	NS

Table 6 – Comparison of S. Creatinine (mg/dl) at various intervals between Infusion + Dopa, Bolus and Infusion groups.

S. Creatinine at-	Infusion + Dopa				Bolus				Infusion				Kruskal–Wallis test applied		
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Chi-square	*p*-value	Difference is-
Baseline	1.33	0.66	0.90	1.00	1.35	0.65	1.20	0.58	1.38	0.72	1.20	0.75	0.061	0.970	NS
24 h	1.33	0.66	1.00	1.10	1.34	0.64	1.10	0.55	1.34	0.66	1.05	0.63	0.266	0.875	NS
48 h	1.26	0.66	1.00	0.70	1.36	0.71	1.10	0.80	1.25	0.57	1.05	0.50	0.930	0.628	NS
72 h	1.25	0.69	0.90	0.70	1.35	0.73	1.15	0.55	1.23	0.60	1.00	0.50	1.794	0.408	NS
7 days	1.33	0.78	1.20	0.80	1.31	0.69	1.10	0.60	1.19	0.50	1.00	0.58	0.426	0.808	NS
30 days	1.19	0.63	0.90	0.60	1.30	0.57	1.20	0.45	1.15	0.50	1.00	0.50	3.958	0.138	NS

potassium levels between the groups and (3) no difference in the number of emergency department visits at one month among the three groups.

The difference between the home dose and dose after 48 h was statistically significant in all the three groups (infusion + dopamine − $p = 0.0066$, bolus − $p = 0.00134$, infusion − $p = 0.00007$). This suggests that patients admitted with acute on-chronic HF required a higher intravenous dose of furosemide as compared to the home dose.

There was a greater loss of fluid in the bolus group between 0–24 h ($p = 0.044$) and in the infusion + dopamine group between 48–72 h ($p < 0.001$). This could be because of a faster initial diuresis in bolus group and peaking of diuretic effect in infusion + dopamine group between 48–72 h. Earlier studies compared either a high versus low dose of diuretic strategy, bolus versus infusion strategy or infusion versus dopamine + infusion strategy. In contrast we compared three different strategies of the same diuretic dose. A Meta analysis by Salvador et al[9] (95%CI 93.1 to 449; $p < 0.01$), and studies by Thomson et al,[10] Pivac et al[11] and Dormans et al[12] showed greater diuresis with continuous infusion than bolus group, but studies by Aaser et al[13] and Schuller et al[14] found no difference between the diuretic effects of the two study groups. Cotter et al[15] studied intravenous low dose dopamine + low dose oral furosemide, intravenous low dose dopamine + medium dose furosemide infusion and high dose furosemide infusion. They found similar urine output in all the three groups. In DOSE trial,[16] 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 ($p = 0.89$), but high dose group had greater diuresis than low dose group ($p = 0.001$). In DAD-HF trial[17] they compared high dose furosemide 20 mg/h continuous infusion versus low dose dopamine 5 μg/kg/min + low dose furosemide 5 mg/h infusion for 8 h. The mean hourly excreted urine volume was similar between the two groups (272 ± 149 ml, 278 ± 186 ml; $p = 0.965$).

In our study, the duration of hospital stay was shorter in the bolus group (mean = 5.03 days; $p = 0.023$). This could be because of rapid initial diuresis leading to early symptomatic improvement and shorter hospital stay. However, other studies showed different results. In DAD-HF trial[17] length of hospital stay were similar in the two groups (mean 5.3 versus 6.1 days; $p = 0.2$). In DOSE trial[16] the length of hospital stay was similar in bolus and infusion group (mean of 5 days; $p = 0.97$). Studies by Thomson et al[10] and Patricia et al[18] showed a shorter hospital stay with continuous infusion. A retrospective analysis by Emad et al[19] had a shorter hospital stay ($p = 0.015$) with infusion + dopamine group. These differences could be due to differences in study design.

Our study showed no statistically significant difference in serum sodium, serum potassium, blood urea and serum creatinine levels at various time intervals between the three groups ($p > 0.05$). In DAD-HF trial,[17] 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. In DOSE trial,[16] there was no significant difference in serum creatinine levels from baseline to 72 h between bolus and infusion group ($p = 0.45$). However, Emad et al[19] observed improvement in serum creatinine ($p = 0.0001$), and an increase in eGFR 57.4 ± 27.4 ml/min with infusion + dopamine as compared to boluses. This could be due to the reno-protective effect.[20] Ungar et al[21] demonstrated a progressive increase in effective renal plasma flow, eGFR and reduction of renal vascular resistance starting from a dopamine dose of 2 μg/kg/min, and peaking at 4 μg/kg/min (+75% and +101% versus baseline, respectively). Elkayam[22] attributed the dilation of large conductance and small resistance renal blood vessels as the cause for increase in renal blood flow.

The number of emergency visits to the hospital for recurrent HF within the first month of discharge was not significant among the three groups ($p = 0.673$). We had two deaths in the bolus and one in the infusion group during the one month follow up. The study population is too small to derive differences in death outcomes. In DAD-HF trial,[17] there was no difference between the groups for all cause rehospitalisation ($p = 0.254$) and all cause mortality ($p = 1.000$) at 60 days.

5. Limitations

1. This was a single blinded, single center study with a small sample size.
2. As patients admitted with ADHF were clinically unstable, baseline weight and eGFR could not be determined. Hence we used blood urea and serum creatinine as a measure to see for worsening renal function.
3. We used a negative fluid balance as a proxy measure of clinical benefit. We did not consider other end points like relief of dyspnea and weight loss.

6. Conclusion

All three modes of diuretic therapies can be practiced with no difference in worsening of renal function and electrolyte levels. Bolus dose administration with its rapid volume loss and shorter hospital stay might be an attractive strategy in our country with limited health resources. However, larger population studies are needed to further evaluate this strategy.

Conflicts of interest

All authors have none to declare.

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