

## Original Research Article

# Comparative study of intravenous diuretics therapy-bolus versus infusion regimen in acute decompensated heart failure

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## ABSTRACT

**Background:** Heart failure (HF) is a growing problem worldwide; more than 20 million people around the world are affected. The objective of the study was to compare the effect of different modes of administration of intravenous diuretic –bolus versus infusion, in acute decompensated heart failure in relation to diuresis and electrolyte balance.

**Methods:** This prospective study was conducted in Darbhanga Medical College and hospital, Laheria sarai between October 2014 to November 2016. Patients of acute decompensated heart failure attending medical emergency ward and Intensive care unit of medicine department of Darbhanga Medical College and hospital, Laheria sarai were selected and grouped randomly as per inclusion and exclusion criteria.

**Results:** The main findings of our study were greater diuresis in the first 24 h of admission with bolus dose. No difference in serum sodium or serum potassium levels between the groups.

**Conclusions:** All three modes of diuretic therapies can be practiced with no difference in worsening of electrolyte levels. Bolus dose administration with its rapid volume loss might be a more effective diuretic strategy in our country with limited health resources.

**Keywords:** Acute decompensated heart failure, Serum sodium, Serum potassium, Intravenous diuretics therapy, Bolus, infusion

## INTRODUCTION

Definition of Acute decompensated heart failure (ADHF) as the sudden or gradual onset of the signs or symptoms of heart failure requiring unplanned office visits, emergency room visits, or hospitalization. Regardless of the underlying precipitant of the exacerbation, pulmonary and systemic congestion due to increased left- and right-heart filling pressures is a nearly universal finding in ADHF.<sup>1</sup>

Specific factors that precipitate HF hospitalization can often be identified, although up to 40% or 50% of ADHF episodes have no known cause.<sup>2</sup> The most common precipitants for HF hospitalization are non-compliance with medications or dietary restrictions, uncontrolled hypertension, ischemia, arrhythmias, and exacerbation of chronic obstructive pulmonary disease with or without

pneumonia.<sup>3</sup> Other contributors include non-cardiac conditions such as renal dysfunction, diabetes mellitus, anemia, and the side effects of medications (NSAIDs, calcium-channel blockers, and thiazolidinediones).<sup>4</sup> The population of India is ageing due to recent successes against communicable diseases such that the number of people >60 years old will increase from 62 million in 1996 to 113 million in 2016.<sup>5</sup> HF is predominantly a disease of the elderly, as the lifetime risk for HF increases with age, so the burden of HF is likely to increase with the ageing population.<sup>6</sup>

The epidemiological transition reflects changes in disease patterns as societies develop. These population and epidemiological transitions are finally reflected in the subsequent health transition, which tracks changes in the health status as populations move from high infant

mortality and fertility rates to low infant mortality and fertility rates. In addition to the ageing the prevalence of hypertension is projected to increase from 118 million (2000) to 214 million (2025).<sup>7</sup>

Diuretic therapy is the standard treatment in emergency rooms and in the cardiac intensive care units. Loop diuretics in the form of bolus doses or continuous infusion are given for the symptomatic relief of acute onset of breathlessness in patient with volume overload presenting as acute decompensated heart failure. The standard justification for the use of continuous infusion of loop diuretics is, to avoid the so called “diuretic resistance”. This term is used when the patients are unable to meet their clinically required decongestive targets despite large doses of loop diuretics.<sup>8</sup> Loop diuretic resistance is likely to be due to the operation of several counter-regulatory processes, including renin angiotensin system (RAAS) which cause fluid retention.<sup>9</sup>

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.<sup>10</sup> 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.<sup>11</sup> 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 study to compare the effect of different modes of administration of intravenous diuretic-bolus versus infusion, in acute decompensated heart failure in relation to diuresis and electrolyte balance.

## METHODS

This prospective study was conducted in Darbhanga Medical College and hospital, Laheria sarai between October 2014 to November 2016. Duration of study was two years. Patients of Acute Decompensated Heart Failure (ADHF) attending medical emergency ward and Intensive care unit of medicine department of Darbhanga Medical College and hospital, Laheria sarai were selected and grouped randomly as per inclusion and exclusion criteria.

### *Method of collection of data*

The patient with ADHF attending medical emergency ward and Intensive care unit of medicine department of Darbhanga Medical College and hospital, Laheria sarai were prospectively enrolled and grouped randomly as per inclusion criteria and exclusion criteria. Ethical clearance was obtained from the institutional ethical committee for the present study.

### *Inclusion criteria*

All patients >18 years old who was hospitalised with signs and symptoms of acute decompensated heart failure.

Patient identified within 24 h of hospital admission. Patients with prior clinical diagnosis of heart failure and on oral diuretics for at least one month. Heart failure was defined by at least one symptom (dyspnea, PND and orthopnea, or oedema) and one sign (rales on chest auscultation, peripheral oedema, ascites) or pulmonary vascular congestion on chest x-ray. The patients who may be planned for intravenous dopamine infusion for heart failure. All patients who gave written consent.

### *Exclusion criteria*

Systolic blood pressure <90 mm Of Hg. Patient presented with noncardiac cause of Heart Failure. Serum creatinine >3 mg/dl at baseline or renal replacement therapy. Patient planned for a procedure requiring intravenous contrast dye during the present admission.

After selection and enrolment of patients they were administered a bolus of intravenous furosemide (40 mg). Then they were randomized into three groups-

Intravenous furosemide infusion (100 mg/24 h) + intravenous dopamine (2.5 mcg/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 [i.e. 5 ampoule of 2ml furosemide =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.

### *Data collection technique*

Patients's 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, pedaledema, ascites, pulse, blood pressure and jugular venous pressure (JVP) were collected. Oxygen saturation (SpO<sub>2</sub>), electrocardiogram (ECG) and pulmonary congestion on chest X-ray was also evaluated. Serum electrolytes were also assessed.

All patients were encouraged to pass urine in a bedside calibrated PAN and those who were not able to do so, underwent Foley's 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 while Secondary end points were negative fluid balance at 48h, 72h, 96h and the trend of serum sodium, serum potassium in the three groups at 24h, 48h, 72h, 7 days and 30 days.

#### Statistical analysis

The information generated from the participants and observations were entered into Statistical package for social sciences (SPSS) 14 following which various statistical analyses were performed Then prospectively collected data of remaining 87 patients, were tabulated and

analysed statistically. Quantitative variables are expressed as means  $\pm$  SD and  $p < 0.05$  was taken as significant.

#### RESULTS

Overall, 90 patients were enrolled for the study. One patient, each expired in the infusion+dopamine group and bolus group during first 24 h of hospitalization and one patient in infusion group got discharged against medical advice within 24h of admission. These three patients were excluded from analysis. After excluding these three patients, we selected 87 patients and all were randomly categorised in three groups.

**Table 1: Demographic data of patient of three study group.**

Demographic data	Infusion+Dopa group (n=29)	Bolus group (n=29)	Infusion group (n=29)	Total (87)	P value
Mean age (years)	56.07 $\pm$ 16.6	59.27 $\pm$ 16.46	59.32 $\pm$ 13.41	58.22 $\pm$ 15.45	0.653
Male	20	23	23	66	0.60
Mean pulse rate (beat/min)	96.33 $\pm$ 36.60	92.93 $\pm$ 17.83	92.40 $\pm$ 24.51	93.88 $\pm$ 27.18	0.793
Mean SBP (mm of Hg)	114.53 $\pm$ 20.03	130.80 $\pm$ 28.81	131.60 $\pm$ 28.47	126.08 $\pm$ 27.21	0.10
Mean DBP (mm of Hg)	69.53 $\pm$ 8.31	80.37 $\pm$ 15.08	84.77 $\pm$ 21.41	77.77 $\pm$ 16.25	0.001

**Table 2: Comparison of Input-Output (I/O) fluid loss (in ml) at various time interval between Infusion+ Dopamine, Bolus and Infusion groups.**

I/O fluid loss at	Bolus group			Infusion group			Infusion + Dopamine group			P value	Difference is -
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median		
0-24 h	-1117.15	726.70	-828	-612.34	447.99	-481.10	-721.57	349.58	-628	0.001	Significant
24-48 h	-752.93	421.62	-751	-702.27	1143.49	-825	-988.67	301.16	-635	0.265	NS
48-72 h	-757.67	500.25	-544	-861.40	720.35	-825	-951.70	397.23	-745	0.394	NS
72-96 h	-688.56	218.72	-755	-763.23	299.00	-645	-722.52	357.09	-800	0.633	NS

Majority of the patients were males (73.3%). The mean age of patients in the present study was 58.22 $\pm$ 15.45 years. Admission BP was 114.53/69.53 $\pm$ 20.03/8.31 mmHg in the infusion+dopamine group, 130.80/80.37 $\pm$ 28.81/15.08

mmHg in the bolus group and 131.60/84.77  $\pm$  28.47/21.41 mmHg in the infusion group. The difference was statistically significant [Systolic blood pressure ( $p = 0.01$ ); Diastolic Blood Pressure ( $p=0.001$ )]. The Baseline clinical data are summarized in Table 1.

**Table 3: Comparison of serum sodium (mEq/l) at various time interval between Bolus, Infusion and Infusion+ Dopamine groups.**

S.sodium at -	Bolus group			Infusion group			Infusion +Dopa group			p-value	Difference is -
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median		
Baseline	133.13	7.65	135	131.2	8.31	132	133.89	5.00	134	0.325	NS
24 h	132.10	7.00	135	131.2	8.76	133	133.37	7.00	135	0.493	NS
48 h	131.31	5.69	132	131.79	6.45	135	133.55	5.00	133	0.287	NS
72 h	131.72	5.40	133	131.82	4.76	133	132.41	5.00	132	0.839	NS
7 days	131.55	4.33	132	131.13	4.07	131	131.62	5.00	130	0.897	NS
30 days	132.62	4.62	134	131.72	3.85	130	133.31	6.00	134	0.500	NS

**Table 4: Comparison of serum potassium (mEq/l) at various time interval between Bolus, Infusion and Infusion+ Dopamine groups.**

S. Potassium at -	Bolus group			Infusion group			Infusion +Dopa group			P value	Difference is -
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median		
<b>Baseline</b>	4.12	0.76	4	4.35	0.93	4.2	4.28	0.80	4.3	0.532	NS
<b>24 h</b>	3.89	0.51	3.9	4.22	0.95	4.1	3.99	0.73	3.9	0.215	NS
<b>48 h</b>	3.82	0.54	3.9	4.0	0.70	3.9	3.86	0.62	3.8	0.502	NS
<b>72 h</b>	3.80	0.54	3.8	4.09	0.55	3.9	3.86	0.51	3.9	0.098	NS
<b>7 days</b>	3.85	0.49	3.9	4.04	0.52	3.95	4.11	0.55	4.0	0.134	NS
<b>30 days</b>	4.01	0.50	4.0	4.01	0.39	4.0	4.19	0.42	4.2	0.221	NS

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 ( $p=0.001$ ), but not statistically significant at other time intervals (24-48 h, 48-72 h, 72-96 h). 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 group. 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 h, 48-72 h and 72-96 h. The fluid loss (in ml) in the Bolus group at 0-24 h, 24-48 h, 48-72 h and 72-96 h was (mean  $\pm$  2SD) 1117.15 $\pm$ 726.70; 752.93 $\pm$ 421.62; 757.67 $\pm$ 500.25; 688.56 $\pm$ 218.72 respectively and the difference was statistically significant ( $p=0.044$ ). The fluid loss in ml in infusion+dopamine group was 612.34 $\pm$ 349.58; 702.27 $\pm$ 301.16; 861.40 $\pm$ 397.23; 763.23 $\pm$ 357.09 respectively and the difference was statistically significant ( $p<0.001$ ). The fluid loss (in ml) in Infusion group was 721.57 $\pm$ 447.99; 988.67 $\pm$ 1143.49; 951.70 $\pm$ 720.35; 722.52 $\pm$ 299 respectively and the difference was statistically not significant ( $p=0.692$ ). Table 2

In bolus group, serum sodium level (in mEq/L) at baseline, 24 h, 48 h, 72 h, 7 days and 30 days was (mean $\pm$ SD) 133.13 $\pm$ 7.65; 132.10 $\pm$ 7.00; 131.31 $\pm$ 5.69; 131.72 $\pm$ 5.40; 131.55 $\pm$ 4.33; 132.62 $\pm$ 4.62 respectively while in Infusion group, it was 131.20 $\pm$ 8.31; 131.20 $\pm$ 8.76; 131.79 $\pm$ 6.45; 131.82 $\pm$ 4.76; 131.13 $\pm$ 4.07; 131.72 $\pm$ 3.85 respectively and in infusion+dopamine group, serum sodium level (in mEq/L) was 133.89 $\pm$ 5.00; 137.00 $\pm$ 7.00; 133.55 $\pm$ 5.00; 132.41 $\pm$ 5.00; 131.62 $\pm$ 5.00; 133.31 $\pm$ 6.00 respectively. There was statistically no significant difference at various time intervals between the three groups. Table 3

Table 4 showed comparison of serum potassium (mEq/l) at various time interval between bolus, infusion and infusion+ dopamine group. In bolus Group, serum potassium level (in mEq/L) at baseline, 24 h, 48 h, 72 h, 7

days and 30 days was 4.12 $\pm$ 0.76; 3.89 $\pm$ 0.51; 3.82 $\pm$ 0.54; 3.80 $\pm$ 0.54; 3.85 $\pm$ 0.49; 4.01 $\pm$ 0.50 respectively while in infusion group, it was 4.35 $\pm$ 0.93; 4.22 $\pm$ 0.95; 4.00 $\pm$ 0.70; 4.09 $\pm$ 0.55; 4.04 $\pm$ 0.52; 4.01 $\pm$ 0.39 respectively and in infusion+ dopamine group, serum potassium level (in mEq/L) was 4.28 $\pm$ 0.80; 3.99 $\pm$ 0.73; 3.86 $\pm$ 0.62; 3.86 $\pm$ 0.51; 4.11 $\pm$ 0.55; 4.19 $\pm$ 0.42 respectively. There was statistically no significant difference at various time intervals between the three groups.

## DISCUSSION

In our study, negative fluid balance was statistically significant between the three groups at 0-24 h ( $p=0.001$ ), but not at other time intervals. 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. Pair wise comparison of fluid loss at 0-24 h between the three groups showed that the difference was statistically significant between infusion+dopamine versus bolus, but not between infusion+dopamine versus infusion or bolus versus infusion groups.

A meta-analysis by Salvador et al, and studies by Thomson et al, Pivac et al, Licata et al and Amer et al showed greater diuresis with continuous infusion than bolus group but Ruchit et al in a prospective study concluded that greater diuresis with bolus dose which are similar as our study.<sup>12-17</sup> In DOSE (Diuretic Optimisation Strategies Evaluation) trial, they compared bolus versus infusion and high dose versus low dose of furosemide.<sup>18</sup> There was no difference in the net fluid loss at 72 h in bolus versus continuous infusion group but high dose group had greater diuresis than low dose group. A randomized clinical trial by Shah et al compared, continuous infusion versus bolus diuretics and found that patient on higher diuretic doses have greater disease severity and may benefits from initial bolus strategy.<sup>19</sup> In DAD-HF trial they compared high dose furosemide (20 mg/h) continuous infusion versus low dose dopamine (5 mg/kg/min) +low dose furosemide (5 mg/h)



infusion for 8 h.<sup>20</sup> The mean hourly excreted urine volume was similar between the two groups.

There was statistically no significant difference for serum sodium, serum potassium at various time intervals between the three groups ( $p > 0.05$ ).

In DAD-HF (Dopamine In Acute Decompensated Heart Failure) trial<sup>20</sup> the laboratory values at 24 h between the two groups were- serum sodium (mEq/l) ( $138 \pm 4$ ,  $138 \pm 4$ ;  $p = 0.593$ ), serum potassium (mEq/l) ( $3.9 \pm 0.4$ ,  $4.2 \pm 0.5$ ;  $p = 0.027$ ), ( $1.25 \pm 0.33$ ;  $p = 0.679$ ). This difference in serum potassium level could be because of the difference in study design.

### Limitation of study

This was a single blinded, single centre study with a small sample size.

### CONCLUSION

So, it is concluded that, all three modes of diuretic therapies can be practiced with no difference in worsening of electrolyte levels. Bolus dose administration with its rapid volume loss might be a more effective diuretic strategy in our country with limited health resources. However, larger population studies are needed to further evaluate this strategy.

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