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Original Research Article

A Comparative Study of Continuous Infusion of Frusemide Vs Intermittent Bolus Administration in Congestive Heart Failure

M.S.Raghuraman[1], A.Saravanavel[2*], K. Jayasingh[3]

[1]Prof & HOD of Anaesthesiology, [2]Post-graduate, [3]Prof. of Medicine,
[*]Dept. of Emergency Medicine,
Aarupadai veedu Medical College, Puducherry, INDIA.

Corresponding Author: M.S.Raghuraman

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ABSTRACT

Background: Frusemide by intermittent intravenous bolus injection has been the first choice of treating patients with pulmonary edema due to heart failure. Although it produces prompt diuresis, the effect on urinary output over time is quite variable and may also result in transient hypotension.
Methods: we conducted a prospective randomized clinical trial comparing the intermittent bolus doses of frusemide (Group B) with continuous infusion of frusemide (Group A) each group comprising 29 patients.
Results: The mean frusemide dose in Group A was 62 mg, which was significantly less when compared to Group B with mean frusemide dose of 157 mg ($P < 0.01$) for achieving the targeted urine output. The mean urine output in Group A was 4062 mL, which was significantly more when compared to Group B with 2764 mL ($P < 0.01$).
Conclusion: We conclude that continuous infusion of frusemide is more beneficial than intermittent bolus doses particularly in hemodynamically labile patients.

Key words: Frusemide, Pulmonary edema, Heart failure, Diuretic therapy

INTRODUCTION

Congestive Heart failure is a clinical syndrome that occurs in patients because of congenital or acquired abnormality of cardiac structure and/or function, develop a constellation of clinical symptoms (dyspnea and fatigue) and signs (edema and rales) that lead to frequent hospitalizations, a poor quality and quantity of life. [1]

Congestive heart failure is a common cause of pulmonary edema which leads to hypoxaemic respiratory failure. Frusemide, usually given by intermittent intravenous bolus doses has been the first choice in treating patients with pulmonary edema due to heart failure. [2] Although bolus frusemide therapy produces prompt diuresis, the effect on urinary output over time is quite variable and may also result in transient hypotension. It is proposed that Continuous infusion results in a more controlled and predictable urinary output. It is also associated with less fluctuation in fluid and electrolyte balance and blood pressure when compared with bolus therapy, which may be advantageous in haemodynamically unstable patients.

Although Heart failure (HF) was once thought to arise primarily in the setting of a depressed left ventricular (LV) ejection fraction (EF), epidemiological studies have shown that approximately one-half of patients who develop HF have a normal or preserved EF (EF >40–50%). Accordingly, HF patients are now broadly categorized into one of two groups: [3]

(1) HF with a depressed EF (commonly referred to as *systolic failure*)

(2) HF with a preserved EF (commonly referred to as *diastolic failure*)

Hypertension is the most common comorbidity in patients presenting with Acute Heart Failure (AHF), and changes in the vasculature of patients with hypertension are well known. [4] Progressive volume overload and acute vasoconstriction are the most common causes of pulmonary edema in AHF.

The initial goals in the management of a patient presenting with AHF are to expeditiously establish the diagnosis, identify the cause and precipitating factors of the heart failure, treat the life-threatening abnormalities, and initiate therapies to provide symptom relief as soon as possible. [4]

In the absence of hypotension, vasodilators play an important role in the initial therapy of patients with pulmonary edema and poor oxygenation, whereas the role of diuretics is more controversial. Systemic volume overload is rarely an emergent issue, although therapy is typically initiated in the emergency department. Seventy five percent of patients in the emergency department receive intravenous diuretics, with a mean door to first intravenous administration time of 2.2 hours according to the study ADHERE. [5] Hospitalization should be considered in patients with worsened congestion, even in the absence of dyspnea and often reflected by significant weight gain (≤5 kg), other signs or symptoms of pulmonary or systemic congestion, newly diagnosed heart failure, complications of heart failure therapy (such as electrolyte disturbances, frequent ICD firings) or other associated comorbid conditions.

When patients have moderate to severe symptoms of heart failure or renal insufficiency, a loop diuretic is generally required. Usual starting dose of furosemide for patients with systolic HF and normal renal function is 40 mg, although doses of 80 to 160 mg are often be necessary to achieve adequate urine output. [6] The first study reported on the administration of frusemide by continuous infusion, published by Lawson *et al* in 1978, demonstrated a marked increase in urinary output in patients with heart failure who failed to respond to oral frusemide. [7] Rudy *et al* concluded that the administration of continuous infusion of diuretics to patients with renal insufficiency affects the loop of Henlé more efficiently than does intermittent injection therapy, with fewer adverse effects. [8] Dormans and co-workers concluded that frusemide administered as continuous infusion is more efficacious than bolus injection and causes less ototoxic side effects in patients with severe heart failure. [9] N Makhoul *et al* concluded that Frusemide administered by continuous infusion results in a higher hourly urinary output, with less hourly fluctuation in output, than does bolus injection. [10]

Review of Salvador DR *et al*, based on small and relatively heterogenous studies, showed greater diuresis and a better safety profile when loop diuretics were given as continuous infusion. [11] Thomson MR et al concluded that the continuous infusion of furosemide was well tolerated and significantly more effective than intermittent furosemide bolus for total urine output. In addition, continuous infusion appears to provide more efficient dieresis. [12]

AIM: To analyse and compare the differences between continuous infusion of frusemide with intermittent bolus administration in patients with acute Pulmonary edema due to Congestive heart failure.

MATERIALS AND METHODS

Design:

Prospective, randomized clinical survey of 58 patients suffering from respiratory failure due to acute pulmonary edema caused by Congestive heart failure. This was conducted in Aarupadai veedu medical college hospital, Pondicherry, India from September 2009 to August 2011.

Inclusion criteria:

Patients admitted with respiratory failure due to acute Pulmonary edema caused by congestive heart failure were included in the study.

A) Congestive heart failure was defined according to following criteria:

i) clinical;
ii) chest X-ray;
iii) Echocardiography.

B) Respiratory failure was defined as SaO2 <90% on room air.

C) Clinical improvement was defined by

1) Normalisation of RR (12 – 20/min)
2) SPO2 > 95%

Exclusion criteria:

1) Serum Creatinine > 2.0 mg / dl
2) Systolic BP < 90 mm of Hg
3) Serum potassium < 3.5 mmol / dl

The patients were randomly divided into two groups.

Group A patients were treated with an initial dose of 1 mg/kg followed by continuous infusion 0.1mg/kg/hr of frusemide for 24 hours, with an option of increasing the dose every 2 hours to a maximum of 0.4 mg/kg/hr if the urine output was less than 1 ml/kg/hr and decreasing the dose if the urine output was more than 4 ml/kg/hr.

Group B patients were treated with intermittent intravenous injection of frusemide at a dose of 0.5 – 1 mg/kg.

Parameters:

The effect of the treatment was examined in both the groups from the initiation of treatment up to 24 hours later, as follows:

1. Systolic and diastolic blood pressure
2. Respiratory rate
3. SPO2
4. Serum potassium (K^+) levels at the initiation of treatment, and after 24 hours.
5. Urine output every hour and total urinary output over 24 hours.
6. Total consumption of frusemide over 24 hours in all groups.

The results were analysed by unpaired Student – t test

RESULTS

Out of 58 patients with CCF studied, the commonest cause for admission was Coronary artery disease constituting 49% (Acute MI 11% and IHD 38%), followed by valvular heart disease 17%. Arrhythmia was the least common cause for admission constituting 3.5%.

The Incidence of Hypotension was more frequent in Group B. 31% of the patients in Group B developed hypotension and the incidence of Hypotension in Group A was 24%. Among the patients who developed hypotension, Pump failure was the commonest cause of hypotension in Group A patients with an incidence of 31%. In Group B patients the commonest cause for hypotension being dehydration 31% and almost equally pump failure with an incidence of 25%.

In our study, out of 16 patients who developed hypotension, 9 (56%) patients required inotropic support. In group A, 5 out of 7 patients who developed hypotension required inotropic support with an incidence of 72%. In Group B, 4 out of 9 patients who

developed hypotension required inotropic support with an incidence of 44%.

The average duration of ICU stay was the same among both the groups. It was 2.65 days in Group A and 2.66 days in Group B. The average duration for normalization of respiratory rate was almost the same among both the groups. It was 15.1 hours in Group A and 15.6 hours in Group B. The average duration for normalization of SpO_2 was almost the same among both the groups. It was 4.7 hours in Group A and 5.3 hours in Group B.

Total of 9 cases out of 58 (16%) required mechanical ventilator support of which 3 were from group A (10%) and 6 were from group B (21%).

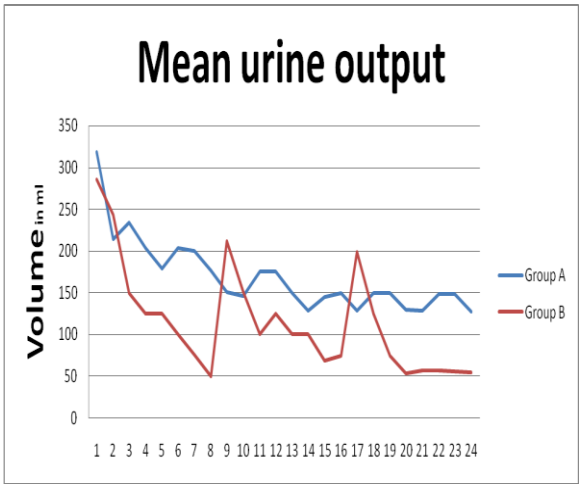
The mean decrease in K^+ in Group A from admission to 24 hours after frusemide administration was 0.44 mEq/L, which is significantly less when compared to Group B with mean decrease in K^+ of 0.62 mEq/L ($P < 0.01$)

Table 1: Mean Frusemide dose

	Mean	S.D	Pooled S.D	t - Value	Mean difference	Confidence limit	Confidence interval
Group A	62	15.44	41.75	8.66	95	66.1 – 123.9	28.9 P<0.01(S)
Group B	157	57					

($P < 0.01$, CI – 95%) (Significant)

The mean frusemide dose in Group A was 62 mg, which is significantly less when compared to Group B with mean frusemide dose of 157 mg ($P < 0.01$) for achieving the targeted urine output.



GRAPH – 1

The Graph - 1 shows that there is much fluctuation in hourly urine output in Group B when compared to Group A. Whenever bolus doses are administered, there is increase in urine output which gradually decreases overtime. But in Group A, the hourly urine output is predictable and almost maintaining a steady state.

Table 2: Mean urine output per day

	Mean	S.D	Pooled S.D	t - Value	Mean difference	Confidence limit	Confidence interval
Group A	4062	285	218	22.67	1298	1146 – 1450	152 P<0.01(S)
Group B	2764	117					

($P < 0.01$, CI – 95%) (Significant)

The mean urine output in Group A was 4062 mL, which is significantly more when compared to Group B with 2764 mL ($P < 0.01$).

DISCUSSION

We compared the effects of frusemide administered by intermittent bolus intravenous injection with continuous intravenous infusion on i) urinary output over a 24-hour period, ii) excretion of electrolytes in the urine, and iii) haemodynamic parameters. We also compared the total consumption of frusemide over a 24-hour period.

Hassalblad V and colleagues, published the ESCAPE trial which concluded that frusemide doses >300 mg/day is associated with increased mortality and poor 6-month outcome. [13] In our study the mean highest dose of frusemide was 162 mg/day and no mortality reported.

Allen LA and colleagues compared continuous infusion *versus* bolus injection of frusemide in post-operative paediatric patients. They showed that continuous infusion increases urinary output with less urinary electrolyte losses, while requiring less drug than the group treated by bolus therapy. [14]

Dormans et al. study of 20 patients with New York Heart Association Class III or IV heart failure of various aetiologies revealed both an increase in daily urinary volume as well as urinary sodium excretion in patients receiving continuous infusion frusemide. [9]

In our study, we found results similar to those reported by the above investigators. [8-14] Frusemide administered by continuous infusion results in a higher hourly urinary output, with less hourly fluctuation in output, than does bolus injection.

Most of the studies quoted in the bibliography were done on post operative patients and critical care settings. We found no previous study on the administration of frusemide in the emergency setting.

Our study shows that administration of frusemide by continuous infusion to patients with respiratory failure due to cardiogenic pulmonary oedema results in an increase in hourly urinary output, with less variability in output, compared to bolus injection therapy in the emergency setting also.

The continuous infusion method is much easier to administer than the bolus method, and is particularly advantageous in the haemodynamically unstable patient, in whom further haemodynamic lability due to sudden increases in urine output after bolus injection is contraindicated.

The continuous infusion method achieves these beneficial results with lower frusemide dose, reiterating that it is the tubular concentration of frusemide that is important rather than the plasma concentration, and thereby decreasing the chances of deleterious effects. Infusion rates should be kept below 4 mg/min to avoid ototoxicity.

CONCLUSION

Our study concludes that both intermittent boluses and continuous infusion of frusemide were successful in treating pulmonary edema and clinical improvement. But the continuous infusion of frusemide in patients with cardiogenic pulmonary oedema results in less variability of hourly urinary output, lesser dose of furosemide, more urine output, less electrolyte disturbance and easy administration compared with the bolus dosing method. Steady urinary output is particularly advantageous in haemodynamically labile patients, and may thus be the preferred method of frusemide administration.

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