Continuous infusion versus intermittent bolus furosemide in heart failure NYHA III-IV

by Samirah Samirah

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Continuous infusion versus intermittent bolus furosemide in heart failure NYHA III-IV

Samirah & S. Sjamsiah
Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

M. Yogiarto
Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
Dr. Soetomo Hospital, Surabaya, Indonesia

ABSTRACT: The study was designed to investigate the therapeutic effect of Continuous Infusion (CI) and Intermittent Bolus (IB) administration of furosemide on patients with NYHA class III-IV heart failure hospitalized in Dr. Soetomo Hospital Surabaya. Thirteen patients received CI of furosemide and 10 patients received IB furosemide. Total urine output, net urine output (nUO/24 h) and urinary sodium excretion were monitored over 24 h. nUO/24 h of IB and CI were 1292 ± 299 mL and 2081 ± 637 mL, respectively. CI group showed significantly higher total urinary output than IB group (3399 ± 793 mL/24 h vs. 2556 ± 343 mL/24 h). The urinary sodium excretion of CI and IB were 302 ± 73 mmol/24 h and 228 ± 58 mmol/24 h, respectively. CI of furosemide resulted in higher total urinary output, net urinary output and urinary sodium excretion than IB furosemide in patients with NYHA class III and IV heart failure.

1 INTRODUCTION

Heart failure is a leading cause for hospitalization of patients older than 65 years. Patients are mostly admitted with dyspnea caused by volume overload. Intravenous loop diuretics are the main treatment for such patients (Palazzuoli et al. 2014). Intermittent bolus (IB) diuretics may cause rapid loss of intravascular volume. This can cause abnormality of electrolyte, renal dysfunction, activation of sympathetic nervous system (SNS) and renin angiotensin aldosterone system (RAAS). This stimulation increases renal sodium level, water resorption and plasma volume. Sympathetic excitation leads to peripheral vasoconstriction, arrhythmia, apoptosis and cardiac remodeling. On the other hand, continuous infusion (CI) can produce sustained and greater diuresis. Thus, intravascular volume fluctuation is minimum, avoiding wide swings in neurohormonal activation and electrolyte imbalance (Amer et al. 2012).

There have been several studies comparing loop diuretic intermitten bolus and continous infusion; however the results are contradictory. A randomized, double-blind study of 308 subjects with ADHF, DOSE, compared high-dose versus low-dose and continous versus intermittent infusion of furosemide. This study did not show positive outcome in either primary and secondary endpoints from regimen comparison. However, there was higher rate of acute kidney injury in the high-dose group (Felker et al. 2011). This result is in line with a randomized study of 41 patients which concluded that there were no considerable differences (Allen et al. 2010). Another randomized, parallel-group study of 56 ADHF patients receiving furosemide compared continuous and intermittent administration. The study concluded that intermittent infusion of furosemide was well tolerated and significantly more effective than intermittent (Thompson et al. 2010). Despite wide use of furosemide in clinical practice, there is as yet no certain guideline to administer furosemide effectively (Salvador et al. 2005). Thus, this study is conducted to evaluate the efficacy and safety of intermittent bolus versus continuous infusion furosemide in a clinical setting.

2 MATERIAL AND METHOD

2.1 *Study design*

This was a single-center, prospective, consecutive study comparing continuous infusion (CI) versus intermittent bolus (IB) of furosemide in patients admitted to Dr. Soetomo Hospital, older than 30 years with clinical diagnosis of NYHA class III and IV heart failure. Ethical clearance was obtained from the ethical committee of Dr. Soetomo hospital. Patients were excluded if creatinine

serum levels were more than 2 mg/dL and if they received non-steroidal anti-inflammatory drugs, with exception of low dose aspirin (<325 mg). Patients were randomized into CI or IB group.

Total daily fluid balance was assessed for 24 h using flow sheets for each subject. Urinary sodium excretion was measured. Blood pressure was assessed three times daily. Electrolyte status and renal function were determined over 24 h. Doses of furosemide used were 60–120 mg.

2.2 *Outcome measurement*

The parameters of efficacy end point were net urine output, total urine output and urinary sodium excretion over 24 h. Net urine output is defined as urine output subtracted by oral plus intravenous (IV) fluid intake. Safety end point parameters were creatinine serum level to monitor the decrease in renal function. Sodium and potassium serum concentrations were assessed. Blood pressure was also monitored for hypotension observation.

2.3 *Data analysis*

All data were analyzed using independent t-test. Variables were presented as mean ± standard deviation and p value < 0,05 was considered significant.

3 RESULT AND DISCUSSION

A total of 23 patients were randomized. There were 10 patients receiving IB and 13 patients receiving CI of furosemide. Baseline characteristics of IB and CI group were not significantly different (Table 1).

Table 1. Baseline characteristics.

	Intermittent bolus (n = 10)	Continuous infusion (n = 13)
Age, mean ± SD (y)	51 ± 13	58 ± 9
Sex, n		
Female	4	4
Male	6	9
Other medication, n		
Spironolactone	9	6
ISDN	6	9
ACE Inhibitor	9	12
Digoxin	4	4
Coronary risk factor (%)		
DM	30	31
HT	60	54
CAD	10	15

Efficacy analysis was done by observing total urine output, net urine output and urinary sodium excretion for 24 h. The total urinary output/24 h in patients receiving IB and CI was 2,556 ± 344 mL and 3,399 ± 79 mL, respectively (p = 0.003; Fig. 1). Net urinary output/24 h of receiving IB and CI group was 1,292 ± 299 mL and 2,081 ± 637 mL, respectively (p = 0.0017; Fig. 1). The urinary sodium excretion/24 h in IB and CI group was 228 ± 58 mmol and 302 ± 73 mmol, respectively (p = 0.016; Fig. 2). Based on the result, there is significant difference in the total urinary output/24 h, the net urinary output/24 h and the urinary sodium excretion/24 h between CI and IB group.

Theoretically, CI of furosemide provides effective level of furosemide to inhibit Na/K/Cl transporter during infusion, resulting in increasing diuresis and natriuresis. Slow input of drug in CI increases secondary response produced by time-course drug delivery to the site of action. A low, but effective, concentration administered continuously increases diuretic effect of furosemide (Meyer 1992, Fergusson 1997, Wittstein 2006).

On the other hand, study by Aaser et al. (1997) found that there is no significant difference in 24 h

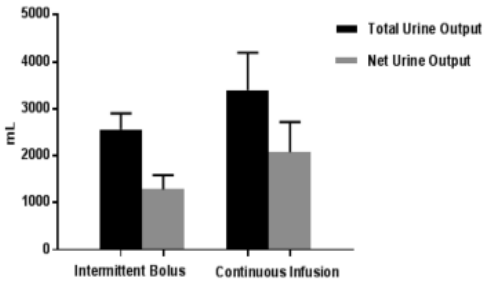

Figure 1. Efficacy end point showed by total urine output and net urine output after continuous infusion (CI) and intermittent bolus (IB) of furosemide.

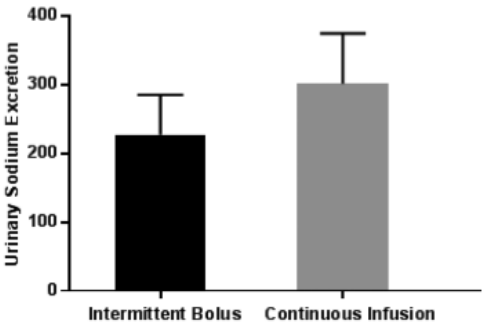

Figure 2. Urinary sodium excretion with intermittent bolus vs. continuous infusion of furosemide.

urine output of patients receiving furosemide CI and IB. However, crossover studies show a greater diuresis in CI as compared to IB administration. A prospective randomized crossover study compared CI and single IV administration of furosemide on nine patients with NYHA class III and IV heart failure. Single dose of 30–40 mg/8 h was used. CI of furosemide was started by loading dose of 30–40 mg, continued with 2.5–3.3 mg/h for 48 h. The 48 h urine output after CI and single IV administration of furosemide was 2,865–6,365 mL (mean value = 3,790 mL) and 3,125–7,365 mL (mean value = 4,490 mL), respectively. Moreover, 48 h urinary sodium excretion for CI and single IV administration were 135–677 mEq and 115–547 mEq, respectively, indicating that 48 h urine output and urinary sodium excretion of CI are higher than single IV dose (Lahav et al. 1992). Another randomized crossover study on 20 patients compared efficacy of IV administration and 8 h infusion of furosemide. Dose used was 250–5,000 mg/24 h. The results showed that there was significant difference in 24 h urine output (CI vs. IV: 2860 ± 240 mL vs. 2660 ± 150 ml). Urinary sodium excretions in CI group and IV group were 210 ± 40 mmol and 150 ± 20 mmol, respectively. Additionally, there were five patients with reversible hearing problems in single dose IV group. Thus, CI might be more effective than single IV, and generated less ototoxicity (Dorman et al. 1996). Study in 56 patients evaluated effectiveness of CI versus intermittent infusion of furosemide and showed that patients receiving CI furosemide exhibit a greater diuresis as compared to those who received intermittent infusion (3,726 ± 1,121 mL/24 h vs. 2,955 ± 1,267 mL/24 h), respectively. This indicates that CI is safer and more effective than intermittent infusion (Thompson et al. 2010). Moreover, the result of the present study supports the previous study, showing that CI of furosemide is more effective than IB administration in patients with heart failure.

CI of furosemide produces less hemostatic effect, and no stimulation to RAAS, SNS and arginine vasopressin, resulting in a better drug response. On the other hand, IB increases renin and sympathetic response, so that the decline in plasma concentration of furosemide decreases blood pressure. However, the present study showed that there is no significant difference between CI and IB in all parameters of safety endpoint, systolic and diastolic blood pressure and heart rate (Table 2).

Single IV administration of furosemide leads to fluctuation of furosemide plasma level (Fergusson 1997). Furosemide can induce diuresis and natriuretic response when the concentration in tubules is adequate to block $Na^+/K^+/2Cl^-$ transporter. There is post-diuretic sodium retention as a compensation mechanism when the urinary furosemide level decreases, usually around 6 h post administration (Bruyne 2003, Ross et al. 2006). In single IV, natriuretic response and sodium retention will reduce the efficacy of furosemide (Fergusson 1997). Post-diuretic sodium retention is an acute diuretic resistance mediated by the activation of RAAS and SNS (Shankar et al. 2003, Wittstein 2006). Single IV dose produces massive diuresis and greater urine volume in a shorter time, leading to sudden decrease in intravascular volume. On the other hand, CI produces smaller reduction in intravascular volume, leading to the consistent increase in urine volume (Fergusson 1997, Bristow 2005).

A study compared furosemide, a short-acting loop diuretic, and azosemide, a long acting loop diuretic, to examine whether CI of furosemide could mimic the effect of long-acting loop diuretic. The report shows that furosemide gives a better improvement on heart rate variability than azosemide. This is due to the fact that furosemide, but not azosemide, stimulates renin release and SNS activity. Furthermore, furosemide, but not azosemide, inhibits the decrease in parasympathetic activity, which is commonly found in heart failure. The inhibition on the decreasing parasympathetic activity during heart failure protects the patient from cardiac sudden death event due to ventricular arrhythmia (Tomiyama et al. 1998).

In the present study, there was no difference in serum sodium, potassium and creatinine level attributed to the side effect of CI and IB administration of furosemide. This finding is in line with the study by Lahav et al. (1992) showing that there is no difference in side effect event. The result of other study evaluating the use of furosemide in patients with severe heart failure and renal insufficiency suggests that CI of furosemide is more effective and gives fewer side effects (Gerlag & Van Meijel 1988).

Table 2. Secondary end point.

	Intermittent bolus (n = 10)	Continuous infusion (n = 13)	p
Δ Systolic blood pressure (mmHg)	12 ± 18	12 ± 20	0.99
Δ Diastolic blood pressure (mmHg)	8 ± 18	17 ± 15	0.377
Δ Heart rate (beats/min)	13 ± 14	10 ± 13	0.508
Δ Serum sodium (mg/dL)	−2.7 ± 7.4	−6.8 ± 11.4	0.333
Δ Serum potassium (mg/dL)	0.3 ± 0.8	0.61 ± 0.9	0.467
Δ Serum creatinine (mg/dL)	0.01 ± 0.26	0.09 ± 0.50	0.647

4 CONCLUSION

The result of the present study suggests that CI of furosemide is more effective than IB administration in patients with NYHA class III and IV heart failure, as shown by the higher total urinary output, net urinary output and urinary sodium excretion after CI of furosemide. It is also suggested that furosemide, either by CI or BI administration, may not affect serum sodium, potassium and creatinine levels.

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