Frusemide Administration in Critically Ill Patients by Continuous Compared to Bolus Therapy

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Abstract

Background: Frusemide is frequently administered to critically ill patients in the intensive care unit (ICU). We investigated whether continuous frusemide infusion therapy was more effective than regular intermittent bolus doses at causing diuresis. Methods: 59 adult patients with fluid overload admitted to two tertiary multidisciplinary ICUs were randomised to either a continuous frusemide infusion or regular intermittent intravenous boluses of frusemide according to pre-defined algorithms aiming for a minimum hourly urine output. Results: There was no significant difference in diuretic response between the two groups during the first 24 h (5.3 liters in the bolus group vs. 5.4 liters in the infusion group). In the bolus group a significantly higher dose of frusemide was needed to achieve target diuresis (24.1 vs. 9.2 mg/h in the infusion group, p = 0.0002). Mean urine output per dose of frusemide was significantly higher in the infusion group (31.6 vs. 18 ml/mg in the bolus group, p = 0.014). At the end of the study, there were no differences in hospital mortality, number of patients requiring ventilatory support, change in serum creatinine or change in estimated glomerular filtration rate. Conclusions: Both intermittent boluses and continuous infusion of frusemide were successful in achieving algorithm-driven diuresis. However, continuous infusion therapy was more effective than intermittent boluses since the dose of frusemide required was significantly less.

Key Words
Congestive heart failure · Drug administration · Fluid overload · Frusemide · Pulmonary oedema

Introduction

Frusemide is commonly used in the intensive care unit (ICU) to promote diuresis in conditions associated with fluid overload or pulmonary oedema, including acute lung injury. Conflicting evidence exists regarding the superiority of continuous frusemide infusion therapy compared to intermittent boluses. Previous studies have been undertaken predominantly in healthy volunteers, patients with congestive heart failure, patients with chronic kidney disease, children after cardiac surgery and premature infants [1–14]. Data for critically ill adult ICU patients are sparse and non-conclusive [15–17].

Our objective was to determine if a continuous frusemide infusion was more effective than regular bolus
doses at producing diuresis in fluid-overloaded adult patients in the ICU. The primary end-point was the difference in the dose required in 24-hour intervals to achieve a target urine output until fluid overload was resolved. In addition we determined whether either mode was associated with a change in renal function or increased need for renal replacement therapy (RRT).

Subjects and Methods

Study Populations

Following approval by the University of Western Ontario Health Sciences Research Ethics Board, all patients admitted to one of two medical/surgical ICUs in a large tertiary referral centre were eligible for the study if they had a clinical condition for which intravenous diuresis was intended and if they fulfilled at least one of the following criteria: (1) radiographic evidence of pulmonary oedema, or (2) clinical signs of volume overload in association with a raised central venous pressure >16 mm Hg or pulmonary capillary wedge pressure >16 mm Hg. These definitions were used to provide a realistic clinical setting with which to test our hypothesis. Exclusion criteria were: documented allergy to sulphonamide or frusemide, age <18 years, pregnancy, pre-existing dialysis-dependent renal failure, indication for urgent RRT, treatment with dopamine or any diuretics unless stopped at the beginning of the study and participation in an investigational drug study. Patients were allowed up to three boluses of any diuretic in the 24 h prior to study enrolment.

Assignment and Blinding

Following informed consent by either the patient or his/her substitute decision maker, patients were randomly assigned to either continuous versus bolus therapy algorithms using sealed, opaque envelopes. The assignment sequence was created using randomly generated numbers. The study was not blinded.

Protocol

Both study groups were treated with frusemide doses based on their lean body weight according to the ‘Devine formula’: lean body weight of females in kg = 45 + 0.91 × (height in cm – 152); lean body weight of males in kg = 50 + 0.91 × (height in cm – 152). The goal was to achieve diuresis aiming for an increase in urine output of at least 50% from baseline and a minimum of 1 ml/kg/h. The baseline urine output was calculated as the mean urine output of the preceding 6 h prior to enrolment into the study. All patients had an indwelling bladder catheter. Frusemide infusion was diluted in 0.9% saline at a concentration of 1 mg/ml. The diuretic doses were chosen to outperform routine clinical practice supported by data from studies in the literature (fig. 1) [13, 15, 18–20]. Patients who had received a bolus dose of frusemide prior to entry into the study and needed further diuresis were started in their allocated randomised algorithm at the next higher dose. If the urine output did not increase by 50% or was less than 1 ml/kg/h during the following 3 h, the bedside nurses were authorised to increase the dose of frusemide according to the assigned algorithm. If the diuretic response after a particular dose was too brisk (i.e. >1.5 litres in 3 h), the dose was reduced to the previous level as indicated in the algorithm. Treatment with frusemide was continued at a dose which was found to be effective until either pulmonary oedema or fluid overload had resolved and diuresis was no longer clinically indicated. Fluid intake was kept to a minimum. Treatment was considered a failure if either the desired urine output could not be achieved despite maximum doses of frusemide or RRT was necessary during the study period.

Study Measurements

Baseline data included: (a) demographics, (b) estimation of severity of illness using the APACHE II [21] and Multiple Organ

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Fig. 1. Frusemide treatment algorithms. a Intermittent bolus therapy. b Continuous infusion therapy.
Dysfunction Score [22], (c) ICU admission diagnosis, (d) duration of ventilation, (e) use of inotropes and (f) mean arterial blood pressure and heart rate. Serum electrolytes and serum urea and creatinine were measured at the beginning and the end of the study. Glomerular filtration rate (GFR) was calculated using the simplified ‘modification of diet in renal disease’ formula [GFR = 186 \times (\text{serum Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})] [23]. In addition, a study sheet was added to the patient’s chart that recorded: (a) hourly and cumulative urine output, (b) hourly and cumulative furosemide dose, (c) duration of study, (d) need for RRT and (e) hospital mortality. Serum electrolytes were measured regularly and corrected if necessary. All other patient management decisions were left to the discretion of the treating ICU team. All bedside nurses were informed about the study and a physician (G.A. or M.O.) was available 24 h a day to answer any questions related to the study protocol. Deviations from the protocol were recorded.

Statistics

All values are presented as means ± SE. Differences in primary outcomes are expressed as differences in means with their corresponding 95% confidence interval. All p values are two sided. Statistical analysis was performed using SPSS software (version 7.0; SPSS, Chicago, Ill., USA). The primary analysis used a Student’s t test to compare the unadjusted means of furosemide dosage and urine volumes in the first 24-hour period. Repeated-measure ANOVA compared baseline variables at the beginning and end of the study period. A target sample size of 43 patients per group was based on a minimum clinically important difference in urine output of 500 ml/24 h (obtained from an informal survey of ICU physicians and nephrologists), a standard deviation of 825 ml/24 h (obtained from a chart review), a significance level of 0.05 and power of 0.80. No interim analysis was planned.

Results

Twenty-seven patients were randomized to the furosemide bolus group and 32 to the infusion group (fig. 2). There were no statistically significant differences in baseline characteristics between the two groups (table 1). Seventeen patients in the bolus group and 18 patients in the infusion group had an estimated GFR ≤ 60 ml/min/1.73 m² before entering the study. Three patients in each group had received a single dose of furosemide before randomisation. Three patients were excluded from intent-to-treat analysis because of missing data for the first 24-hour period (1 patient in the bolus group and 2 patients in the infusion group). Thus, the primary intent-to-treat analysis was performed on 26 patients in the bo-

Table 1. Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bolus group (n = 27)</th>
<th>Infusion group (n = 32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60 ± 3.3</td>
<td>68 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female ratio²</td>
<td>15/12</td>
<td>16/16</td>
<td></td>
</tr>
<tr>
<td>Baseline urine output³, ml/h</td>
<td>60 ± 6</td>
<td>70 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Serum urea, mmol/l</td>
<td>11.3 ± 1.0</td>
<td>10.6 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine, µmol/l</td>
<td>136 ± 11</td>
<td>123 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>55 ± 5.3</td>
<td>62 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>20–126</td>
<td>13–125</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>95 ± 4</td>
<td>97 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>82 ± 3</td>
<td>81 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>18.9 ± 1.3</td>
<td>19.7 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>MODS score</td>
<td>6.7 ± 0.4</td>
<td>7.7 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Patients on inotropes</td>
<td>1 (3.7%)</td>
<td>6 (19%)</td>
<td></td>
</tr>
<tr>
<td>Patients on ventilator¹</td>
<td>22 (81.5%)</td>
<td>23 (71.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Days on ventilator</td>
<td>4.5 (n = 22)</td>
<td>7.3 (n = 23)</td>
<td></td>
</tr>
<tr>
<td>ICU admission diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI or CABG</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
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<td>5</td>
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<td>3</td>
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</tr>
<tr>
<td>Trauma</td>
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<td>2</td>
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</tr>
<tr>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Neurological disease</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

All values are presented as means ± SE. CABG = Coronary artery bypass surgery; eGFR = estimated GFR according to the ‘modification of diet in renal disease’ formula; MI = myocardial infarction; MODS = Multiple Organ Dysfunction Score; NS = nonsignificant (p ≥ 0.05).

¹ Based on the previous 6 h.

² Including 1 patient on non-invasive ventilation in each group.

Fig. 2. Patient flow through the study.
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lus group and 30 patients in the infusion group. Twenty-one patients in the bolus group and 25 patients in the infusion group achieved target diuresis and resolution of fluid overload. In 25 patients, this target was achieved within 24 h of therapy (14 patients in the bolus group and 11 patients in the infusion group), the remaining 21 patients needed frusemide for >24 h. In both groups, 3 patients discontinued frusemide therapy early before fluid overload was fully resolved: in the bolus group, 1 patient was started on dopamine, 1 patient had excessive diuresis which responded to discontinuation of frusemide and in 1 patient a decision was made to withdraw all therapy; in the infusion group, 1 patient stopped frusemide because of a cardiac arrest which was not related to electrolyte abnormalities, 1 patient needed emergency surgery and 1 patient stopped due to severe hypotension which responded to fluid boluses. Two patients per group were classified as ‘treatment failures’: in the infusion group, 2 patients with an acute myocardial infarction and congestive heart failure achieved diuresis above target in the first 48–72 h during the study period, but diuresis tailed off afterwards despite the presence of ongoing oedema and maximum doses of frusemide. In contrast, 2 patients in the bolus group only passed 25–30 ml/h in the first 15–18 h despite increasing doses of frusemide. Their admission diagnoses were acute ventricular septal defect and ischaemic bowel. Both had impaired renal function before entering the study as judged by an estimated GFR of 21 and 29 ml/min/1.73 m², respectively.

Infusion and bolus therapy achieved similar diuresis in the first 24-hour interval (5.4 vs. 5.3 litres, respectively; p = 0.64). Patients in the infusion group received a mean frusemide dose of 9.2 mg/h (SD 5.05) compared to 24.1 mg/h (SD 19.26) among patients in the bolus group (p = 0.0002; fig. 3). Similarly, the urine volume per dose of frusemide administered was significantly higher in the infusion group compared to the bolus group (31.6 vs. 18 ml/mg, p = 0.014). Frusemide doses and urine volumes beyond 24 h were not statistically different, but the number of patients remaining in the study at these intervals was small (fig. 3).

The changes in serum creatinine between beginning and end of frusemide therapy were similar in both groups (table 2). Only 1 patient in the bolus group required haemodialysis during the study period. Nine patients in the infusion group and 10 patients in the bolus group remained ventilated at the end of the study. Mean length of stay in the ICU was longer in the infusion group (15.4 days, SD 17.94) compared to the bolus group (8.9 days, SD 8.68), but hospital mortality was similar in both groups (33% in the bolus group and 34% in the infusion group).

Heart rate and mean arterial pressure changed significantly during the study period. However, there was no difference between the two groups and all variables

**Table 2. Changes in renal function whilst on frusemide therapy**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Bolus group</th>
<th>Infusion group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in serum creatinine, μmol/l</td>
<td>+8 ± 28.0</td>
<td>+10 ± 21.7</td>
</tr>
<tr>
<td>Range</td>
<td>−40 to 97</td>
<td>−29 to 67</td>
</tr>
<tr>
<td>Change in eGFR, ml/min/1.73 m²</td>
<td>−4 ± 10.0</td>
<td>−2.3 ± 12.7</td>
</tr>
</tbody>
</table>

eGFR = Estimated GFR according to the modification of diet in renal disease formula [23].

![Figure 3](image-url) Renal responsiveness: frusemide doses (a) and urine volumes (b). Thirty, 15 and 6 patients were examined at 0–24, 24–48 and 48–72 h in the infusion group and 26, 8 and 4 patients in the bolus group, respectively.
changed in the same direction. The incidence of arrhythmias was similar among patients enrolled in the study compared to patients not participating. The 4 patients who failed the frusemide algorithm despite maximum doses all died in the ICU. Their diagnoses on admission to ICU were ‘ischaemic bowel’ and ‘new ventricular septum defect’ in the 2 bolus group patients, and ‘coronary bypass surgery’ and ‘abdominal aortic aneurysm repair’ in the patients in the infusion group.

We observed four protocol violations: one in the bolus arm and three in the infusion arm. One patient in the bolus group missed a dose but received double the next scheduled time, not altering the total amount given in the first 24 h. One patient in the infusion arm received double the intended dose, only altering his total dose by 20 mg of frusemide. Two further patients in the infusion group received extra doses of frusemide, both outside the initial 24-hour window.

**Discussion**

Our study demonstrated that both regular boluses of frusemide and continuous infusion of frusemide achieved adequate and comparable diuresis in most critically ill patients. However, when administering frusemide by continuous infusion a significantly lower dose was required.

Frusemide is widely used in the clinical arena, the main indications being the promotion of diuresis and natriuresis to resolve conditions of fluid overload [24]. Frusemide is also often used to either prevent emerging acute renal failure (ARF) or to convert oliguric renal failure to non-oliguric renal failure [19]. A large observational study by Uchino et al. [25] confirmed that 70% of 1,743 ICU patients with ARF received diuretic treatment of which frusemide was the most commonly prescribed drug (98.3%). Diuretic use was not associated with higher mortality. In contrast, investigators of the PICARD study group showed that the use of diuretics in critically ill patients with ARF was associated with an increased risk of death and non-recovery of renal function [26]. A recently published meta-analysis concluded that frusemide conferred no significant clinical benefits in the prevention and treatment of ARF in adults [27]. In contrast, in patients with acute lung injury, treatment with frusemide has been shown to improve lung function resulting in a shortened duration of mechanical ventilation and shorter ICU stay but no difference in mortality [28].

The best mode of frusemide therapy remains unclear. Studies performed in the non-ICU setting suggest that continuous infusion therapy might be superior to intermittent boluses, but these studies are small and often not randomised. Pivac et al. [3] demonstrated greater diuresis in patients with congestive heart failure when a single dose of 40 mg was given by infusion compared to bolus. Dormans et al. [1] studied higher doses of frusemide in patients with severe congestive heart failure and found that an 8-hour continuous infusion resulted in 25% higher urine volumes compared to an equal dose of frusemide given as a single bolus. All cases of reversible hearing loss occurred in the bolus group. van Meyel et al. [4] investigated 10 patients with congestive heart failure (NYHA class III and IV) who were resistant to a daily dose of 250 mg frusemide and found that a continuous infusion of frusemide, titrated gradually from 20 to 160 mg per hour, led to a substantial increase in mean sodium excretion. Salvador et al. [7] summarised the results of eight randomized controlled studies on continuous versus intermittent treatment with loop diuretics in congestive heart failure in a systematic review. They found that currently available data were insufficient to make definite recommendations for clinical practice but acknowledged that some small and relatively heterogenous studies showed greater diuresis and a better safety profile when loop diuretics were given as continuous infusion [7].

Data on the merits of the two administration methods in critically ill patients is even more sparse. Only three studies focused on adult ICU patients. Copeland et al. [16] randomised 18 adult post-cardiac surgery patients to 2 bolus injections of frusemide (0.3 mg/kg) or a frusemide infusion at 0.05 mg/kg/h for 12 h. At the end of the study period there were no significant differences in urine output and urinary Na⁺ and K⁺ excretion between both groups. Similarly, Mojtahedzadeh et al. [17] randomised 22 patients with pulmonary oedema or fluid overload to either continuous frusemide infusion or intermittent boluses of frusemide and found that both regimens were equally effective in achieving a negative fluid balance. However, a continuous infusion of frusemide resulted in more controlled diuresis with less haemodynamic and electrolyte alterations. Schuller et al. [13] randomised 33 critically ill adult patients with pulmonary oedema or fluid overload to either a frusemide infusion or individually adjusted regular frusemide boluses aiming for a urine output of at least 1 ml/kg/h. At the end of the 24-hour study period, there were no significant differences in the cumulative frusemide dosage used, net fluid loss or length of stay in the ICU and hospital. Interestingly, they also
analysed the data of 12 patients who met all inclusion criteria but were not included in the study and found that this group of patients, who had been treated with diuretics according to the discretion of the attending physicians, had received significantly less frusemide compared to both randomised groups (166 vs. 430 mg/24 h). Their net diuresis was less and more importantly, their length of stay in the ICU and hospital was significantly longer than that of patients who underwent protocol-guided diuresis. Schuller et al. [13] concluded that both continuous and bolus diuretic regimens were equally effective in achieving negative fluid balance. Like Schuller et al. [13], we observed no difference in total diuresis between the infusion and bolus group, which is not too surprising since the algorithms in both studies were designed to achieve a minimum target urine output. In fact, the average urine outputs were also similar (around 5 l/24 h in their study vs. 5.3 l/24 h in our group). However, in contrast to their study, we observed a significant difference in the mean doses of frusemide between both groups. While patients in our infusion group only needed 9.2 mg/h, their infusion group required on average 450 mg frusemide in 24 h (i.e. ~18.8 mg/h) despite being actively fluid restricted. In the bolus group, the mean doses of frusemide were similar in both studies (24.1 mg/h vs. 447 mg/24 h, i.e. 18.6 mg/h). The exact reason for the discrepancy in the dose of frusemide in the infusion group is not immediately clear. Potential differences in the actual treatment algorithm and in patient characteristics may have played a role. Patients in our study may have been sicker as judged by a higher APACHE II score (19.3 vs. 14.5) and a higher proportion of patients on mechanical ventilation (76 vs. 18%). In the study by Schuller et al. [13], the majority of patients suffered from congestive heart failure (26/33). They also used a more aggressive upward titration of the infusion rate if urine output was not met.

We did not observe any differences in adverse events between bolus and infusion therapy despite the differences in dosages used. In particular, there was no difference in the degree of renal dysfunction between both groups. Oto- and vestibular toxicity, a problem associated with high doses or rapid infusion of frusemide, was not identified in any of our patients but was not specifically assessed when the patients were discharged from the ICU. Serum electrolytes were checked on a regular basis and any abnormalities were corrected quickly, but we did not record the incidences of hypokalaemia and hypomagnesaemia.

Our study did not investigate the exact reasons why frusemide infusion therapy was more effective than regular boluses. In principle, frusemide acts on the thick ascending loop of Henle in the kidney and blocks active reabsorption of chloride and sodium. Overall response to frusemide depends on the delivery of the drug to its intratubular site of action, the dynamics of interaction with its receptor and whether or not solutes are reclaimed more distally. It has been shown that inbetween bolus doses, effective concentrations may quickly dissipate to levels that are insufficient to block Na⁺ reabsorption, which may be the reason why bolus doses are less effective [29]. In addition, distal tubular Na⁺ reabsorption increases in response to natriuresis [30]. The degree of this compensatory Na⁺ retention correlates with the rate and magnitude of natriuresis, which is generally greater after a bolus dose.

We acknowledge some shortcomings of our data. Our study was randomised but not blinded. Blinding would have resulted in patients receiving an infusion (frusemide or placebo) as well as regular boluses (frusemide or placebo) concomitantly, which would have led to the administration of an additional 250 ml of fluid. This could have potentially caused problems in patients who were already volume overloaded. However, the outcome measures were objectively determined, and the analysis was performed on the intention to treat. One patient in the bolus group and 2 patients in the infusion group had missing data for the primary analysis, but all other randomised patients were included. Patients were not actively fluid restricted but fluid intake was kept to a minimum. The sample size was less than originally planned because the principal investigators of the study left the institution. However, the observed difference and variance in urine output indicate that achieving our intended enrolment would likely not have affected our current findings. The 95% confidence interval of our results (~1,867 to 1,722 ml/24 h) includes our proposed minimally important difference of urine output of 500 ml/24 h. A sample of 1,062 patients per group would have been required to demonstrate equivalence using this minimally important difference. Lastly, we did not check for signs of oto- or vestibular toxicity and did not record the total fluid balance and the frequency of electrolyte disturbances.

Despite these limitations, to our best knowledge this is the largest study confirming that protocol-driven continuous diuretic therapy is effective in ICU patients. The inclusion and exclusion criteria in our study were quite liberal resulting in a wide spectrum of patient diagnoses which makes the results applicable to most multidisciplinary ICU patients. We demonstrated that continuous frusemide affords the benefit of requiring lower doses...
compared to intermittent bolus therapy with the potential benefit of reducing adverse side effects. In the absence of clear guidelines on how to best manage fluid overload in critically ill adults, we recommend protocol-driven infusion diuretic therapy. Like any other treatment, this should be guided by the patient’s response, clinical judgment, meticulous attention to detail and frequent assessment of the patient’s ever-changing clinical condition.

References


Ostermann/Alvarez/Sharpe/Martin

Ostermann/Alvarez/Sharpe/Martin