Goal-directed diuresis: A case — control study of continuous furosemide infusion in critically ill trauma patients

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ABSTRACT

Background: Excessive crystalloid administration is common and associated with negative outcomes in critically ill trauma patients. Continuous furosemide infusion (CFI) to remove excessive fluid has not been previously described in this population. We hypothesized that a goal-directed CFI is more effective for fluid removal than intermittent bolus injection (IBI) diuresis without excess incidence of hypokalemia or renal failure. Materials and Methods: CFI cases were prospectively enrolled between November 2011 and August 2012, and matched to historic IBI controls by age, gender, Injury Severity Score (ISS), and net fluid balance (NFB) at diuresis initiation. Paired and unpaired analyses were performed to compare groups. The primary endpoints were net fluid balance, potassium and creatinine levels. Secondary endpoints included intensive care unit (ICU) and hospital length of stay (LOS), ventilator-free days (VFD), and mortality. Results: 55 patients were included, with 19 cases and 36 matched controls. Mean age was 54 years, mean ISS was 32.7, and mean initial NFB was +7.7 L. After one day of diuresis with CFI vs. IBI, net 24 h fluid balance was negative (−0.55 L vs. +0.43 L, \( P = 0.026 \)) only for the CFI group, and there was no difference in potassium and creatinine levels. Cumulative furosemide dose (59.4mg vs. 25.4mg, \( P < 0.001 \)) and urine output (4.2 L vs. 2.8 L, \( P < 0.001 \)) were also significantly increased with CFI vs. IBI. There were no statistically significant differences in ICU LOS, hospital LOS, VFD, or mortality. Conclusions: Compared to IBI, goal-directed diuresis by CFI is more successful in achieving net negative fluid balance in patients with fluid overload with no detrimental side effects on renal function or patient outcome.

Key Words: Crystalloids, diuresis, furosemide, trauma
Loop diuretics are the most commonly prescribed diuretics in the Intensive Care Unit (ICU) setting, and they work by blocking chloride reabsorption in the ascending loop of Henle. The subsequent reabsorption of sodium and water passively follow the chloride ion. Importantly, all diuretics (except spironolactone) must reach the luminal side of the nephron in order to exert their action. In addition, the drug concentration must exceed a minimum threshold concentration at that site of action to evoke a response. Above this threshold, the diuretic response increases with increasing dose up to a maximum response, at which point escalating drug doses only serve to increase toxicity without diuretic benefit. The goal of diuretic therapy, then, should be to maintain luminal drug concentrations somewhere between the minimum threshold and the maximum response for as long as possible. The extent of diuretic response is also dependent upon the time course of drug delivery to the active site. Intermittent bolus dosing is associated with peaks and troughs and variability of luminal drug concentration, resulting in substantial time spent below the minimum threshold of efficacy. Theoretically, continuous infusion dosing results in a lower peak serum concentration, with more consistent drug delivery and urine output. This may translate into reduced risk of renal failure, ototoxicity, or electrolyte derangements. Studies in healthy volunteers have concluded that an intravenous (IV) bolus is the least efficient mode of administration and that controlled infusion at maximum efficiency could increase diuretic response up to 2.3 times higher.

It has previously been reported that the use of furosemide in critically ill, fully resuscitated trauma patients is safe and effective in promoting diuresis. However, the optimal mode of delivery has not been adequately investigated. In clinical practice, intermittent bolus dosing results in brisk, immediate diuresis, but this effect soon wears off, and the degree of fluid removal is often sub-optimal, especially when repeat dosing is reliant upon physician discretion. A nurse-driven continuous infusion protocol, on the other hand, may enhance overall diuretic use when explicit diuresis goals are stated at the outset and strict parameters guide subsequent dose adjustments. Similar nurse-driven protocols for heparin and insulin infusion have been in long-standing use and are widely accepted as superior to dosing based on individual physician discretion. In 2011, we developed a sliding scale continuous furosemide infusion (CFI) protocol that stated a daily net negative fluid balance goal (−600 to −2000 mL) at the outset. With the end point set in advance, we were thus able to calculate the necessary hourly net negative fluid balance required to achieve that goal and adjust the CFI accordingly. The aim was to achieve more reliable and consistent diuresis with less variability in urine output and potentially less hemodynamic swings. We hypothesized that the use of a protocolized CFI is safe and more effective in fluid removal than intermittent bolus injection by physician discretion in diuretic-naive, fully resuscitated, fluid overloaded critically ill trauma patients.

**MATERIALS AND METHODS**

**Design**

This is a prospective case-control study in which we compared patients that were treated following the new CFI protocol (CASES - CFI) with contemporaneous patients who received intermittent bolus injection of furosemide guided by physician discretion (CONTROLS - IBI). The cases were prospectively enrolled from November 2011 to August 2012. These patients were matched to controls at a 1:2 ratio. Matching criteria were age (±10 years), gender, Injury Severity Score (ISS) (±10), APACHE 2 score (±3), and net fluid balance at the initiation of diuresis (±2.5 L).

**Protocol development**

Based on our review of the literature as well as our hospital data, we developed the CFI protocol. Within our division, we reached consensus on the addition of this protocol to daily practice in which diuresis based on physician discretion had been the standard of care. The inclusion criteria for patients to enter the CFI study group were: Admission to the surgical ICU, an attending physician judgment that the patient needed diuresis, age >18 years, >5.0 L net fluid positive since ICU admission, anticipated ICU length of stay >24 h after initiation of diuresis, and a hemodynamically stable status (defined as mean arterial pressure >60 without vasopressor requirement for >12 h, heart rate (HR) <120, and base deficit > −3).

The CFI protocol began with a 10 mg IV furosemide loading dose, followed by an initial infusion rate of 2 mg/h. After 4 h (and every 4 h thereafter), the net fluid balance was assessed for underachievement, overachievement, or target diuresis. If the net negative fluid balance was under the stated goal, an additional 10 mg IV loading dose was given, and the infusion rate was increased by 1 mg/h. If the net negative fluid balance was over the stated goal, the infusion was temporarily discontinued for 1 h and resumed at a rate 1 mg/h less than the previous rate. No changes were made if the target diuresis was achieved (Figure 1). In the IBI group, furosemide was prescribed as per usual clinical practice in diuretic-naive patients; initial doses were usually 10 mg or 20 mg IV, and subsequent doses were given at the clinician’s discretion.

Safety parameters for discontinuation of the GDD protocol are stated in Figure 2. Serum potassium levels were monitored twice a day and aggressively replaced as per standard of care.

**Data collection**

Data collection included baseline demographics (age, gender, race), mechanism of injury, surgical diagnosis, comorbid medical conditions, physiologic parameters (such as systolic blood pressure, mean arterial blood pressure, HR, urine output, and net fluid balance), laboratory data (creatinine, potassium, blood gas), and clinical outcomes. The primary outcomes of interest were the total milligrams of furosemide and total urine output for the 1st day of diuresis. Secondary outcomes included net 24 h fluid
balance, hospital and ICU length of stay (LOS), ventilator-free days (VFD), and mortality.

**Statistical analysis**

We compared the CFI (cases) and IBI (controls) groups to identify differences in patient characteristics and outcomes. Continuous variables were summarized using mean ± standard deviation and compared by Student’s t-tests, or summarized using median with interquartile and compared by Wilcoxon rank sum tests, whichever appropriate. Categorical variables were compared by Fisher’s exact test. Statistical significance was considered as a two-sided $P < 0.05$. All statistical analyses were performed using SAS version 9.3 (The SAS Institute, Cary, NC, USA). This study was approved by our Institutional Review Board (no. 2011P002771) and complies with the ethical standards laid down in the 1964 declaration of Helsinki and its later amendments.

**RESULTS**

Fifty-five patients were included, with 19 CFI cases, and 36 IBI controls matched 1:2 except for two patients for whom second IBI controls could not be found. For CFI cases, mean age was 54 years, mean ISS was 32.7, and mean initial TBB was +7.7 L. After 1-day of diuresis with CFI versus IBI, net 24 h fluid balance was negative ($-0.55$ L vs. $+0.43$ L, $P = 0.026$) and potassium and creatinine values were not significantly different. Cumulative furosemide dose ($59.4$ mg vs. $25.4$ mg, $P < 0.001$) and urine output ($4.2$ L vs. $2.8$ L, $P < 0.001$) were significantly increased in the CFI group, compared with the IBI group, and vital signs before and after initiating diuresis were not significantly different in both groups. There were no statistically significant differences in ICU or hospital LOS, VFD, $\text{PO}_2/\text{FiO}_2$ (P/F) ratio or mortality [Table 1].

**DISCUSSION**

In this case — control study, we report that the use of protocolized CFI, or goal-directed diuresis, resulted in significantly more furosemide administration with resultant more diuresis and net negative fluid balance when compared with diuresis directed by physician discretion and intermittent bolus injection. It is reassuring to note that in both groups, vital signs were not affected, and usual clinical parameters of acute kidney injury (blood urea nitrogen, creatinine) were likewise unchanged.

Although our study focused exclusively on critically ill injured patients, our results are consistent with those in other studied populations, mainly cardiac surgery and congestive heart failure patients. Two meta-analyses of randomized controlled trials in patients with acute decompensated heart failure have demonstrated superior weight loss with CFI compared to IBI.

**Table 1: Demographics and outcomes**

| Demographics and outcomes | Cases ($n = 19$) | Controls ($n = 36$) | $P$ |
|---------------------------|-----------------|-------------------|----|
| Age, mean (SD)            | 54 (20)         | 54 (20)           | 0.97 |
| Male, number (%)          | 18 (95)         | 34 (94)           | 0.99 |
| ISS                       | 32.7 (12.6)     | 30.7 (9.2)        | 0.55 |
| TBB at diuresis initiation (L), mean (SD) | 7.7 (3.7)       | 7.2 (4.1)         | 0.61 |
| $\Delta$Na, mean (SD)     | 0.42 (3.83)     | 0.71 (4.38)       | 0.80 |
| $\Delta$K, mean (SD)      | 0.10 (0.48)     | 0.12 (0.90)       | 0.90 |
| $\Delta$BUN, mean (SD)    | 1.53 (2.97)     | 1.57 (3.39)       | 0.97 |
| $\Delta$Cr, mean (SD)     | 0.003 (0.094)   | 0.038 (0.224)     | 0.42 |
| $\Delta$pH, mean (SD)     | 0.02 (0.06)     | 0.05 (0.08)       | 0.13 |
| $\Delta$base excess, mean (SD) | 2.83 (1.30)   | 2.04 (2.99)       | 0.19 |
| $\Delta$P/F, median (Q1-Q3) | -7.5 (-70 to 62) | -23 (-101 to 24.5) | 0.38 |
| TBB day 0 (L), mean (SD)  | 2.42 (1.86)     | 2.64 (2.18)       | 0.70 |
| Cumulative furosemide (mg), day 1, mean (SD) | 59.4 (30.5)     | 25.4 (32.0)       | <0.001 |
| Urine output day 1 (L), mean (SD) | 4.2 (1.2) | 2.8 (1.5)         | <0.001 |
| Net 24 h fluid balance (L), mean (SD) | -0.55 (1.07) | 0.43 (2.09)       | 0.026 |
| Hospital LOS (d), median (Q1-Q3) | 20 (15-33) | 25.5 (20-24.5) | 0.29 |
| ICU LOS (d), mean (SD)    | 14.5 (10.6)     | 11.3 (6.3)        | 0.20 |
| VFDs (d), mean (SD)       | 13.2 (9.9)      | 15.2 (9.1)        | 0.47 |
| Mortality, number (%)     | 3 (16)          | 7 (19)            | 0.99 |

ISS: Injury severity score; TBB: Total body balance; Na: Sodium; K: Potassium; BUN: Blood urea nitrogen; Cr: Creatinine; BE: Base excess; PO$_2$: Oxygen partial pressure; FiO$_2$: Fraction of inspired oxygen; P/F: The ratio of arterial oxygen concentration to the fraction of inspired oxygen; LOS: Length of stay; ICU: Intensive care unit; VFD: Ventilator-free day; SD: Standard deviation.
without any significant differences in electrolyte imbalances or side effects.\textsuperscript{[14,15]} Trials in cardiac surgery have similarly reported improved diuretic efficiency with continuous infusion compared to bolus dosing: More negative fluid balance, decreased time to extubation, and significantly decreased oxygen requirements with fewer alterations in cardiac index and filling pressures.\textsuperscript{[11,16,17]} In one report, cardiac index, central venous pressure, and diastolic pulmonary artery pressures remained unchanged and vasopressor support requirements decreased, despite an average of 5.7 L of urine output over a 24 h period.\textsuperscript{[15]} CFI was also shown to be superior to bolus injection (at the same overall dose) in patients with chronic renal insufficiency, despite a six-fold lower peak plasma drug concentration.\textsuperscript{[18,19]} Drug-induced myalgias occurred exclusively during bolus injection dosing.

In a randomized trial of 22 MICU patients with pulmonary edema or fluid overload, Mojtahedzad reported that CFI, compared to bolus injection, was more effective in promoting diuresis and improved P/F ratio and had fewer dramatic changes in HR and potassium concentrations.\textsuperscript{[20]} Salvador et al. reported in a systematic review of eight randomized trials (\textit{n} = 254) that CFI dosing resulted in greater diuresis and a better safety profile (less tinnitus and hearing loss) when compared to bolus injection.\textsuperscript{[21]}

However, not all studies have shown CFI superiority.\textsuperscript{[22,23]} A randomized study of protocolized continuous infusion versus protocolized bolus injection furosemide in mixed medical-surgical patients was terminated early for futility when interim analysis showed the equivalency of net diuresis.\textsuperscript{[24]} The serum creatinine was significantly more increased in the bolus group though. The authors also compared enrolled protocolized patients (of either arm) with nonrandomized, nonprotocolized patients, and reported significant differences in net cumulative fluid balance (\(-4.5 \text{ L vs. } -1.3 \text{ L}\)), attributed to less cumulative furosemide dose (diuretic efficiency). For those patients who survived to discharge, protocolized diuresis significantly decreased ICU and hospital LOS. The act of protocolization, rather than a mode of delivery, appeared to drive the superior outcomes in this study.

It is important to note that if a CFI is to be employed, it should be accompanied by a loading dose to achieve drug levels quickly above minimum efficacious threshold. Without this loading dose, the onset of diuresis is delayed approximately 3 h.\textsuperscript{[11]} A meta-analysis of continuous versus intermittent dosing of loop diuretics in hospitalized patients concluded that superior urinary output and weight loss occurred only in trials where a loading dose preceded the continuous infusion.\textsuperscript{[25]}

Our study has several limitations that must be acknowledged. First, this was not a randomized trial and therefore there may be unmeasured confounders, despite our best attempts to match the cases to controls. For example, the mere act of protocolization itself, rather than the continuous infusion, may have been the reason for the increased furosemide administration and diuresis. At the time of this study, we did not have a protocol for intermittent injections and hence we could not test this hypothesis. Regardless, we do not feel that this significantly detracts for the conclusion that protocolization resulted in significantly more diuresis than individual discretion. Secondly, the compliance with the protocol as written was not strictly enforced. Once the CFI protocol was initiated, clinicians were free to deviate. When this occurred, it was almost always early cessation of the infusion (in the absence of laboratory or clinical derangements). Stricter adherence to the protocol may have led to more dramatic differences between groups. Other protocol deviations, such as absent loading dose and inappropriate dose de-escalations, were common as well. However, in this early experience with CFI in this patient population, we felt it prudent to allow protocol deviations. Rather than quantify and catalog each deviation, we chose instead to analyze the patients on an intention-to-treat basis rather than per-protocol. As such, it is important to emphasize that our analysis and conclusions are on the strategy of goal-directed diuresis using CFI and not the flawless implementation of the protocol. This allowance reflects actual practice and increases external validity. Thirdly, we did not continue data collection beyond the first 24 h after initiating furosemide in either group. The reason for this is because we found that many patients had their infusion discontinued between the 2\textsuperscript{nd} and 4\textsuperscript{th} day of diuresis. We allowed the clinicians to discontinue the infusion once adequate diuresis (in their judgment) was complete. Fourthly, the sample size is admittedly small and therefore there is a risk of type 2 statistical error. Our study is underpowered to detect differences in clinically meaningful outcomes such as ventilator-free days, complications (pulmonary, gastrointestinal, cardiac, infectious, etc.), ICU or hospital LOS, and mortality. Our findings should be interpreted with caution and should be viewed as hypothesis-generating for future adequately powered studies. Nevertheless, this preliminary description of the use of protocolized furosemide infusion demonstrates proof of concept in this patient population and we have found our protocol to be generally well-tolerated and effective in attaining the goal of achieving negative fluid balance. At our own institution, we have become more comfortable with the protocol with increasing experience and continue to use it in appropriately selected patients.

**CONCLUSION**

In significantly fluid overloaded, ICU trauma patients, goal-directed diuresis using a protocolized continuous furosemide infusion results in increased fluid removal without demonstrable morbidity.

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