

## Prospect of Bumetanide Infusion in Treatment of Congestive Heart Failure

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### ABSTRACT

This editorial summarizes available data on the efficacy of diuretic strategies given by bolus or as continuous infusion in congestive heart failure (CHF). Either mode of diuretic therapy helps in relieving congestion. Question remains unresolved whether continuous infusion is more efficacious compared to bolus diuretic in preserving renal function and reducing re-hospitalization rate. In author's study continuous bumetanide infusion in CHF is very effective in producing large volume of urine, rendering symptomatic relief and preserving or even improving renal function. Long term study in a large number of patients could answer re-hospitalization rate and mortality.

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**Key words:** Diuretic Therapy; Bolus Diuretic; Diuretic infusion; Bumetanide Infusion; Congestive Heart Failure; Relief of Shortness of Breath

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### EDITORIAL

Patients with congestive heart failure (CHF) are frequently hospitalized for acute decompensation, associated with volume overload and increased shortness of breath<sup>[1]</sup>. In these patients, diuretic therapy is considered as first line of therapy, according to American College of Cardiology/ American Heart Association guidelines for management of CHF<sup>[2]</sup>. An important objective of management in CHF is to optimize therapy for stabilization and a shorter hospital stay with lower rates of complications and readmission into the hospital. The presence of volume overload with a positive fluid balance constitutes an important prognostic factor that is usually associated with poor outcome. Thus intravenous diuretic administration has become the mainstay of therapy for the volume overload associated with acute decompensated heart failure (ADHF)<sup>[3]</sup>.

For volume resolution, different protocols of diuretic therapy in CHF have been used, with the two main strategies including continuous infusion and boluses. Results show that both therapies are effective when trying to achieve a negative fluid balance in patients with volume overload, with some data indicating superiority of furosemide infusion over boluses<sup>[3]</sup>. Although a meta analysis suggested greater urine output, shorter length of hospital stay, less renal impairment, and lower mortality rate with continuous infusion compared with intermittent bolus dosing<sup>[4]</sup>, the dose (diuretic optimization strategies evaluation) trial called these findings into question<sup>[5]</sup>.

The Dose Trial is the largest prospective double blind randomized trial of ADHF to evaluate initial diuretic strategies<sup>[5]</sup>. There was no significant difference in either of the co-primary end points of global assessment of symptoms of change in serum creatinine over 72 h with diuretic administration either by bolus or continuous infusion or with a low dose versus a high dose strategy. Taken as a whole the data suggest that higher doses of diuretics are likely to be more efficacious in relieving congestion than a low dose strategy, at the cost of transient worsening of renal function that does not appear to have long term consequences<sup>[5]</sup>.

Indeed an optimal method to achieve high and sustained renal diuretic concentration may be a bolus followed by continuous infusion to achieve immediate and sustained effects<sup>[6]</sup>.

Given the need for rapid onset of action, loop diuretics are typically given intravenously for hospitalized ADHF patients. Although loop diuretics are commonly given by intermittent intravenous bolus, there are potential benefits of continuous infusion<sup>[7]</sup>. Continuous infusion results in a more constant delivery of diuretic to the renal tubules, potentially reducing post-diuretic “rebound” sodium retention and maintaining a more consistent diuresis.

Hitherto, published articles are in agreement that diuretic therapy is the cornerstone of management in CHF with volume overload requiring repeated hospitalization for relief of shortness of breath. However, there is no consensus in efficacy between bolus diuretic and continuous diuretic infusion as an optimum therapy for CHF with volume overload<sup>[5]</sup>. However, continuous intravenous infusion of a diuretic is considered more efficacious compared with intermittent bolus dosing<sup>[4]</sup>. The latter is consistent with author’s own observation consisting of continuous infusion of bumetanide. In author’s study protocol, bumetanide infusion consists of bumetanide 12 mg or 24 mg mixed in 500 ml ½ normal saline or 5% dextrose solution and is delivered at a rate of 21 ml/hour for 96 hours. Thus bumetanide is delivered intravenously at a constant rate of 0.5 mg or 1 mg per hour. As urine flow increases typically from day 2 of the infusion, replacement fluid in the form of normal saline with potassium chloride 20 to 40 meq per liter bag is administered concomitantly with bumetanide infusion. The rate of replacement fluid is adjusted between 60 and 100 ml/hour depending upon urine flow rate and change in renal function during the course of bumetanide infusion. The replacement fluid is similar to that in venovenous ultra filtration method. Without replacement fluid renal function will decrease rapidly especially in those with existing renal failure and will consequently decrease the urine flow rate. Full attention must be paid to electrolytes including magnesium changes and development of metabolic alkalosis.

Here is an example to that effect: A 88 years white female was admitted into a local hospital in April 2009 with a diagnosis of anasarca, CHF, lung cancer treated with chemotherapy and acute renal failure. She was so massively edematous that she could not move her legs: they were lying on the bed like logs of wood. Her home medications were Lisinopril 10 mg P.O. daily and furosemide 40 mg P.O. twice daily. Initial laboratory studies showed BUN 84 mg/dL, serum creatinine 2.32 mg/dL with eGFR of 21 mL/min. Lisinopril and furosemide were discontinued and she was treated with continuous bumetanide infusion 12 mg mixed in 5% dextrose solution with delivery of 0.5 mg bumetanide per hour. Her urine output rapidly increased ranging from 3800 ml day 1, to 7300 mL day 2, to 9000 mL day 3, 6600 mL day 4, and 11050 mL on day 5. She produced 37750 mL or 37.75 liters of urine in 5 days. Average urine output per day was 7500 ml. At the end of bumetanide infusion she was freely able to move her legs, breath normally, and eat well. Her renal function improved as shown below.

Bumetanide infusion in CHF as described in author’s study is very efficacious in relieving shortness of breath, unloading fluid overload

**Table 1 Advantage, Disadvantage, and Pitfalls of Diuretic Therapy in CHF**

	Before Infusion	After Infusion
BUN (mg/dL)	85	75
Serum Creatinine (mg/dL)	2.32	1.41
eGFR (ml/min)	21	38

and rendering them asymptomatic. Definitely renal function improves in every patient. Thus replacement fluid with additive of potassium chloride is the key to preservation of kidney function and prevention of electrolyte imbalance and metabolic alkalosis. However, salutary effect of bumetanide infusion in a limited number of patients is inadequate to predict re-hospitalization rate and long-term mortality. However, no immediate mortality is noted in author’s study. Further meager literature information with regard to bumetanide infusion does not permit to support or refute author’s study. Nevertheless, discontinuation of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) drug which most patients with CHF receive before bumetanide infusion is a reasonable explanation for much higher urine output (up to 11 liters/day) observed in author’s patients when compared to other studies. For instance in the UNLOAD study, net fluid loss (L) at 48 hours was 4.6 liter with ultrafiltration, 3 liter with IV bolus diuretic and 3.9 liter with IV continuous diuretic<sup>[8]</sup>. In this study 49% patient with ultrafiltration, 52% with bolus diuretic and 44% patients with continuous diuretic received ACEI and a smaller number in each group also received ARB. These drugs decrease renal perfusion and cause azotemia<sup>[9,10]</sup>. Thus with the use of ACEI/ARB drugs, delivery of diuretics to the renal tubules is decreased, hence potency of diuresis is attenuated.

Coinciding with author’s own observation, other authors have stated that higher doses of diuretics are likely to be more efficacious in relieving congestion than a low-dose strategy<sup>[7]</sup>. Still other authors have used low dose dopamine (5 µg/kg/min) to enhance the effect of diuretic but observed no additive benefit<sup>[11]</sup>.

In European guidelines on heart failure, diuretics are recommended for the relief of dyspnea and edema in patients with signs and symptoms of congestion, irrespective of left ventricular ejection fraction, with stated aim of achieving and maintaining euvoemia with least achievable dose of diuretic<sup>[12]</sup>.

Finally, in Cochrane Heart Group, the effects and adverse effects of continuous intravenous infusion of loop diuretics were compared with those of bolus intravenous administration among patients with CHF class III-IV. The authors concluded based on small or heterogeneous studies greater diuresis and better safety profile when loops diuretics were given as continuous infusion. However, larger studies should be done to settle this issue<sup>[13]</sup>.

In summary, diuretics remain the mainstay of first line therapy in acute decompensated heart failure. However, deficiencies exist. They are (1) bolus vs continuous infusion; (2) furosemide vs bumetanide. No head to head study is ever done to compare efficacy of diuretic, with regard to symptomatic relief, re-hospitalization rate and mortality between furosemide and bumetanide. However, author’s study convincingly endorses continuous infusion of bumetanide as an alternative to dialysis therapy in patients with CHF with fluid overload and advanced renal failure.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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