

## Review Article

# Furosemide in Acute Kidney Injury – A Vexed Issue

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## Abstract

Loop diuretics have been traditionally used to enhance renal excretion of excess salt and water. Loop diuretics have numerous reno-protective properties that may help improve the management of Acute kidney injury and subsequently patient outcomes. Given the improved prognosis of non-oliguric acute kidney injury, it may be tempting to use loop diuretics in oliguric acute kidney injury to improve the urine output. A review of literature shows that the use of loop diuretics in patients with acute kidney injury has been associated with inconclusive results despite the theoretical benefits. Here we review the concerns pertaining to the use of furosemide in patients with Acute kidney injury.

**Keywords:** Furosemide; Acute kidney injury; Outcomes

## Introduction

Acute Kidney Injury (AKI) is characterized by an abrupt decrease in renal function with subsequent accumulation of nitrogenous waste products [1,2]. Presentation of AKI can vary from a subtle increase in serum creatinine to anuric renal failure [1,2]. Despite significant clinical advances in the field of medicine, the morbidity and mortality associated with acute kidney injury remains high [3-5]. AKI can have systemic manifestations, and may contribute to the dysfunction of vital organs including the heart, lungs, liver and brain. Therefore primary prevention and early diagnosis of acute kidney injury are crucial in improving patient outcomes.

The most common cause of AKI is acute tubular necrosis, accounting for around 45 % of hospital acquired acute kidney injury [6]. Incidence of acute tubular necrosis is particularly high in the ICU, and mortality of critically ill patients can approach 80 % [6]. AKI can be classified according to a rise in serum creatinine concentration or based on urine output. This carries a prognostic significance. Non-oliguric Acute kidney injury (urine output >500ml/day) is known to be associated with an improved overall prognosis compared to oliguric (urine output < 500ml/day) acute kidney injury [7,8].

Hypo-perfusion induced AKI is one of the most common causes of acute kidney injury. This may sound perplexing considering the fact that the kidney is a highly vascular organ. Most of the blood flow to the kidney is diverted to the renal cortex to optimize glomerular filtration. The medulla by contrast has reduced blood flow, possibly to preserve osmotic gradients and enhance urinary concentration [9]. Medullary hypoxia under normal conditions has been documented in several mammalian species, including humans. The medullary partial pressure of oxygen is in the range of 10 to 20 mm Hg, contrasting with the partial pressure of oxygen in the cortex, which is about 50 mm Hg [10]. It is therefore not surprising that following episodes of hypoxia or ischemia, the medulla has a high likelihood of injury. During periods of ischemia, there is evidence that the thick ascending limb of the loop of Henle and the S3 segment of the proximal tubule in the outer medulla are preferentially damaged [11]. Interestingly, in response to hypoxia and ischemia, the thick ascending limb cells produce non-prostaglandin cytochrome P450 arachidonic acid metabolites which reduce activity of the luminal Na-K-Cl2 transporter [12]. This may

be protective, as a decrease in cellular transport may cause reduced energy consumption, thus possibly preserving cell viability.

## Insight into the world of loop diuretics

The most common loop diuretics used clinically are furosemide, bumetanide and torsemide. Furosemide is a weak organic acid, cleared mainly by the kidneys, half of which is actively secreted in an unchanged form by organic acid transporters in the proximal tubule [13]. Furosemide is a highly protein bound drug (>98 %), which facilitates tubular secretion and its action [13]. Therefore a reduction in the fraction of furosemide bound to proteins or presence of another highly protein bound drug (such as warfarin or phenytoin) may reduce tubular secretion of furosemide, and hence its diuretic effect.

The site of action of furosemide is the Na-K-Cl2 co-transporter at the intraluminal side of the ascending loop of Henle. The effects of furosemide depend on its concentration in the urine, time of delivery to its site of action and the response of the loop of Henle [13]. Concentration of furosemide in the urine can be reduced in the presence of other organic acids that compete for the organic acid transporters in the proximal tubules [13], and by drugs such as Probenecid, Ciprofloxacin and Cephalosporins. Patients with acute kidney injury may have a reduced response to furosemide due to multiple mechanisms including a reduced tubular secretion of furosemide and blunted response of Na-K-Cl2 co-transporters at the loop of Henle [13].

Loop diuretics were traditionally used to enhance renal excretion of excess salt and water. Blunting the Na-K-Cl2 transporters by the loop diuretics helps decrease cellular transport and reduces energy consumption and hence possibly preserving cellular viability. This mechanism of loop diuretics may be protective in acute kidney injury [14]. Loop diuretics may also improve urine flow by flushing out debris and denuded epithelium, thus avoiding intratubular obstruction. They may also reduce the back leak of glomerular filtrate into the renal interstitium which tends to worsen acute kidney injury [14-16]. Loop diuretics have been shown to decrease renal vascular resistance and therefore increase renal blood flow. This is likely due to the inhibition of prostaglandin dehydrogenase by loop diuretics, resulting in diminished breakdown of PGE 2 (a potent vasodilator),

subsequently resulting in decreased renal vascular resistance and increased renal blood flow [17]. Based on these physiological rationales, loop diuretics have been used increasingly in patients with acute kidney injury. Given the improved prognosis of non-oliguric AKI, it is tempting to use loop diuretics in oliguric AKI to improve the urine output.

Furosemide has been used in an effort to try to minimize the risk of contrast induced nephropathy. Although the results for the studies showing that furosemide use for the prevention of AKI are inconclusive, *Merenzi et al* in a prospective randomized trial showed a significantly lower incidence of AKI in patients treated with hydration and furosemide vs those treated with hydration alone [18].

### Outcomes of loop diuretic use

A systemic review and meta-analysis [19] published in 2007 evaluated 65 studies, including 5 randomized control trials. A total of 555 patients were evaluated and analyzed. Only two of the trials included critically ill patients, while the quality of these trials was assessed to be low. There was no statistical difference in mortality or renal recovery with use of loop diuretics compared with control. However, loop diuretics were associated with a shorter duration of renal replacement therapy, shorter time to spontaneous decline in serum creatinine level and a greater increase in urine output from baseline. Insufficient data were available on acid-base status, hospital length of stay or health costs. Four studies reported toxicity, most commonly transient tinnitus and deafness.

A cohort study done by *Mehta et al* [20] (PICARD study group) from 1989 to 1995 enrolled 552 patients with acute renal failure in intensive care units at 4 medical centers associated with the University of California. Diuretics were used in 326 patients (59%) at the time of nephrology consultation. Patients treated with diuretics on or before the day of consultation were older and more likely to have a history of congestive heart failure, nephrotoxic (rather than ischemic or multifactorial) origin of acute renal failure, acute respiratory failure, and lower serum urea nitrogen concentrations. With adjustment for relevant covariates and propensity scores, diuretic use was associated with a significant increase in the risk of death or non-recovery of renal function (odds ratio, 1.77; 95% confidence interval, 1.14-2.76). The risk was magnified (odds ratio, 3.12; 95% confidence interval, 1.73-5.62) when patients who died within the first week following consultation were excluded. Increased risk was borne largely by patients who were relatively unresponsive to diuretics.

*Uchino et al* [21] conducted a prospective, multiple-center, multinational epidemiologic study involving intensive care units from 54 centers and 23 countries. 1743 patients were enrolled who either were treated with renal replacement therapy or fulfilled predefined criteria for acute renal failure. Three multivariate models were developed to assess the relationship between diuretic use and subsequent mortality. Approximately 70% of patients were treated with diuretics at study inclusion. Severe sepsis/septic shock (43.8%), major surgery (39.1%), low cardiac output (29.7%), and hypovolemia (28.2%) were the most common conditions associated with the development of acute renal failure. Furosemide was the most common diuretic used (98.3%). Combination therapy was used in 98 patients only. In all three models, use of diuretics was not associated with a significantly increased risk of mortality.

*Hager et al* [22] at an Eastern Switzerland hospital conducted a randomized, double blind placebo controlled trial to determine the effect on renal function of post-operative continuous, intravenous furosemide after major thoraco-abdominal or vascular surgery. Furosemide (1 mg/hour) or placebo was administered to 121 consecutive patients admitted to the intensive care unit after major abdominal, chest or vascular surgery and continued throughout the intensive care treatment period. Enrollment was performed during a 6 months period. No patients were excluded. Renal function was determined serially by measuring creatinine clearances and plasma creatinine concentrations. Postoperatively, creatinine clearance decreased significantly to 83% (furosemide) and to 81% (placebo group) of the initial value. This decrease was not affected significantly by furosemide. Retrospective subgroup analysis using stepwise regression also did not show any differences between the groups. Hypokalemia was detected in 36% (furosemide) versus 19% of the blood sample (placebo,  $p = 0.006$ ). The study concluded that low-dose intravenous furosemide appeared to offer no advantage over placebo in an unselected group of patients with moderate postoperative renal impairment. As no patients with acute renal failure necessitating dialysis were observed during the study period, the effect of furosemide in more severe postoperative renal impairment and the effects of higher doses of loop diuretics remained unknown.

A meta-analysis by *KM Ho* [23], evaluated 9 randomized control trials with a total of 849 patients. Outcome measures not significantly different after furosemide treatment included in-hospital mortality, risk for requiring renal replacement therapy or dialysis, number of dialysis sessions required and proportion of patients with persistent oliguria. Stratifying studies that used furosemide to prevent or treat acute renal failure did not change the results on mortality and the risk for requiring dialysis. Evidence suggested an increased risk of temporary deafness and tinnitus in patients treated with high doses of furosemide.

### Impediment for loop diuretic use

Furosemide may result in the aggregation of Tamm-Horsfall protein in the tubular lumen as it results in acidification of urine. This can subsequently result in intratubular obstruction [24]. Furosemide can acidify the urine, and acidic urine may potentially result in formation of methemoglobin casts in patients with severe intravascular hemolysis [25], which are potentially nephrotoxic and may result in further renal impairment. Use of loop diuretics without assessment of underlying cause of acute kidney injury may result in worsening of renal parameters. Use of higher doses of furosemide is often needed in patients with acute kidney injury. This however may increase risk of ototoxicity, especially as the clearance of furosemide is severely reduced in acute kidney injury [26]. High doses of furosemide may also result in vasoconstriction which may be harmful for patients with myocardial dysfunction [27].

### Conclusion

While there is a role for the use of diuretics in the ICU for management of volume overload, the evidence for using diuretics to convert oliguric AKI into non-oliguric AKI is lacking. Despite the fact that the use of loop diuretics may improve urine output, there is not significant evidence that use of loop diuretics reduces mortality, need for dialysis, length of hospital stay or improves renal recovery.

There is in fact concern that its use in some clinical scenarios may actually be harmful. Although in theory loop diuretics have plenty of reno-protective qualities and physiological benefits of use that is not the case thus far concluded after the review of the literature in patients with AKI. We need to await further randomized controlled studies to evaluate the use of loop diuretics in AKI.

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