KDIGO Clinical Practice Guideline for Acute Kidney Injury

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Chapter 3.4: The use of diuretics in AKI

Diuretics are frequently used in patients at risk of AKI, and in the management of those who develop AKI. Since fluid overload is one of the major symptoms of AKI, diuretics are often used for patients with AKI to facilitate fluid management. Recent observational studies showed that 59–70% of patients with AKI were given diuretics at the time of nephrology consultation or before the start of RRT. In addition, oliguric AKI has a worse prognosis than nonoliguric AKI and physicians often prescribe diuretics to convert oliguric to nonoliguric AKI. Diuretics are also used to control fluid balance and permit administration of nutrition and medications. Furthermore, several diuretics have potentially renoprotective effects that might prevent development of AKI and hasten its recovery. However, diuretics can also be harmful, by reducing the circulating volume excessively and adding a prerenal insult, worsening established AKI. Therefore, it is essential to evaluate usefulness of diuretics to improve outcome of patients with AKI, not just for fluid management.

3.4.1: We recommend not using diuretics to prevent AKI. (1B)

3.4.2: We suggest not using diuretics to treat AKI, except in the management of volume overload. (2C)

RATIONALE
Loop diuretics have several effects that may protect against AKI. They may decrease oxygen consumption in the loop of Henle by inhibiting sodium transport, thus potentially lessening ischemic injury. Loop diuretics act at the luminal surface of the thick ascending limb of the loop of Henle and inhibit the Na-K-2Cl cotransporter, resulting in a loss of the high medullary osmolality and decreased ability to reabsorb water. Inhibition of active sodium transport also reduces renal tubular oxygen consumption, potentially decreasing ischemic damage of the most vulnerable outer medullary tubular segments; therefore, furosemide might protect kidneys against ischemic injury. Furosemide also might hasten recovery of AKI by washing out necrotic debris blocking tubules, and by inhibiting prostaglandin dehydrogenase, which reduces renovascular resistance and increases renal blood flow. Based on these properties, loop diuretics might be expected to prevent or ameliorate AKI. However, there are only minimal data to support this theory, and there is some evidence of harm associated with loop diuretic use to prevent or treat AKI. Furosemide is the most commonly prescribed diuretic in the acute-care setting, and a number of RCTs have tested whether furosemide is beneficial for prevention or treatment of AKI. Specifically, prophylactic furosemide was found to be ineffective or harmful when used to prevent AKI after cardiac surgery, and to increase the risk of AKI when given to prevent CI-AKI. Epidemiologic data have suggested that the use of loop diuretics may increase mortality in patients with critical illness and AKI, along with conflicting data that suggest no harm in AKI. Finally, furosemide therapy was also ineffective and possibly harmful when used to treat AKI.

There is no evidence that the use of diuretics reduces the incidence or severity of AKI. Ho et al. conducted two comprehensive systematic reviews on the use of the loop diuretic frusemide (furosemide) to prevent or treat AKI. Furosemide had no significant effect on in-hospital mortality, risk for requiring RRT, number of dialysis sessions, or even the proportion of patients with persistent oliguria. Results from the most recent review are shown in Figure 9 and Figure 10.

The primary prevention studies included patients who underwent cardiac surgery, coronary angiography, and major general or vascular surgery. In two of these studies, all participants had mild pre-existing renal impairment. Two of the three studies reported mortality in patients randomized to furosemide (n = 103) vs. placebo (n = 99), with a pooled RR of 2.67 (95% CI 0.75–7.25; P = 0.15). All three studies reported RRT incidence in patients randomized to furosemide (n = 128) vs. placebo (n = 127), with a pooled RR of 4.08 (95% CI 0.46–35.96; P = 0.21). Thus, subanalysis to separate primary and secondary prevention trials did not alter the conclusion that, within the sample size limitations of this study, furosemide is not effective for the prevention of AKI.

The systematic review and meta-analysis by Ho and Power also included six studies that used furosemide to treat AKI, with doses ranging from 600 to 3400 mg/d (Figure 9 and Figure 10). No significant reduction was found for in-hospital mortality or for RRT requirement. The largest single study of furosemide for treating AKI was conducted by Cantarovich et al., which included 338 patients with AKI requiring dialysis. Patients were randomly assigned to the administration of either furosemide (25 mg/kg/d i.v. or 35 mg/kg/d orally) or placebo. Although time to reach 2 l/d of diuresis was shorter with furosemide (5.7 days) than placebo (7.8 days, P = 0.004), there was no difference in survival and number of dialysis sessions. At present, the current evidence does not suggest that furosemide can reduce mortality in patients with AKI.

Furosemide may, however, be useful in achieving fluid balance to facilitate mechanical ventilation according to the
lung-protective ventilation strategy in hemodynamically stable patients with acute lung injury. On the other hand, the literature also suggests that high-dose furosemide (>1 g/d) may cause ototoxicity. In the first meta-analysis by Ho and Sheridan, high doses of furosemide (range 1–3.4 g/d) caused deafness or tinnitus more frequently than the control (RR 3.97; 95% CI 1.00–15.78; \( P = 0.05 \)). When administered as continuous infusion a dose of 0.5 mg/kg/hour was not associated with ototoxicity. Taken together with several small studies showing that the prophylactic use of diuretics to prevent AKI actually increased AKI incidence, these data raise significant concerns regarding use of loop diuretics to prevent or treat AKI in any setting. We similarly conclude that there is no evidence that the use of loop diuretics reduces the severity of AKI, or improves outcomes in this syndrome. Although the use of loop diuretics in early or established AKI facilitates management of fluid balance, hyperkalemia, and hypercalcemia, and is indicated for these clinical purposes, any putative role in the prevention or amelioration of AKI course is unproven.

Two recent studies have investigated whether the administration of furosemide to patients treated with CVVH could be associated with a more rapid discontinuation of the dialysis therapy. van der Voort et al., observed, as expected, an increased urinary volume and sodium excretion, but this intervention did not lead to a shorter duration of renal failure...
or more frequent renal recovery. The second study by Uchino et al. analyzed data from the B.E.S.T. kidney and found that, from a total of 529 critically ill patients who survived during CRRT, 313 patients were removed successfully from CRRT while 216 patients needed “repeat RRT” after temporary discontinuation. Urine output (during the 24 hours before stopping CRRT) was identified as a significant predictor of successful cessation, but the predictive ability of urine output was negatively affected by the use of diuretics. Thus, a beneficial role for loop diuretics in facilitating discontinuation of RRT in AKI is not evident.

**Mannitol**

Mannitol has been frequently used in the past for prevention of AKI; however, most of the studies are retrospective, underpowered, and, overall, the studies did not meet the criteria of the Work Group to be included in formulation of recommendations. Prophylactic mannitol has been promoted in patients undergoing surgery. While in most of these instances mannitol increases urine flow, it is highly probable that mannitol does not convey additional beneficial effects beyond adequate hydration on the incidence of AKI.

In radiocontrast-induced nephropathy, loop diuretics and mannitol in one study have been shown to exacerbate ARF. Weisberg et al. randomized patients undergoing contrast-medium investigations to receive saline or one of three renal vasodilator/diuretic drugs (dopamine [2 µg/kg/min], mannitol [15 g/dl in a one-half isotonic saline solution given at 100 ml/h] or atrial natriuretic peptide). Dopamine, mannitol, and atrial natriuretic peptide were associated with a much higher incidence of renal dysfunction in diabetic subjects compared to patients receiving saline alone.

Mannitol is often added to the priming fluid of the cardiopulmonary bypass system to reduce the incidence of renal dysfunction, but the results of these studies are not very convincing. Two small randomized trials—one in patients with pre-existing normal renal function, the second in patients with established renal dysfunction—did not find differences for any measured variable of renal function. More convincing are the results obtained with the preventive administration of mannitol, just before clamp release, during renal transplantation. The sparse controlled data available have shown that 250 ml of mannitol 20% given immediately before vessel clamp removal reduces the incidence of post-transplant AKI, as indicated by a lower requirement of post-transplant dialysis. However, 3 months after transplantation, no difference is found in kidney function compared to patients who did not receive mannitol.

It has also been suggested that mannitol is beneficial in rhabdomyolysis by stimulating osmotic diuresis and by lowering the intracompartmental pressure in the affected crushed limbs; again, these studies were either not randomized or underpowered. A separate guideline on crush injury associated with disasters, mainly earthquake victims, is under preparation by the ISN Renal Disaster Relief Task Force.

In summary, despite experimental animal data and the anecdotal human evidence for the beneficial effects of mannitol, there are no adequately powered prospective RCTs comparing mannitol vs. other strategies. Based on these considerations, the Work Group concludes that mannitol is not scientifically justified in the prevention of AKI.

**RESEARCH RECOMMENDATION**

- Given the potential to mitigate fluid overload but also to worsen renal function and possibly cause kidney injury, further study is required to clarify the safety of loop diuretics in the management of patients with AKI.