Loop Diuretics and Mortality in Patients with Acute Kidney Injury

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21.1 General Principles

Intensive care unit (ICU) patients are often at high risk of fluid retention not only due to underlying conditions such as heart or liver failure but also because they often receive multiple additional intravenous infusions of crystalloids and colloids, including parenteral nutrition, to manage their critical disease [1–3]. Loop diuretics are often used for prevention or treatment of volume overload in patients with or at risk for acute kidney injury (AKI). In addition to the management of fluid imbalance, other acknowledged indications for administration of diuretics in the critically ill include hyperkalemia, hypercalcemia, hyperazotemia, and all their clinical sequelae [1–3].

Since fluid overload is associated with worse clinical outcomes (see Chap. 19), any measure employed to avoid it could potentially improve survival [4, 5]. However, fluid management should be very careful in patients with AKI as overaggressive diuresis may lead to decreased cardiac preload and act adversely on the kidneys. Both hypovolemia (regardless of left ventricle function) and low cardiac output (even with normo- or hypervolemia) result in inadequate renal perfusion, which leads to adrenergic stimulation and activation of the renin-angiotensin system. The resulting vasoconstriction in the renal cortex causes redistribution of renal blood flow in favor of the vulnerable medulla. Hence, the use of diuretics in the setting of AKI should be extremely considerate [6]. Moreover, hemodynamic optimization should be sought whenever possible [7], and fluid management should be guided by the measurement of volume responsiveness using appropriate methods (i.e., central/

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mixed venous oxygen saturation, esophageal Doppler, dynamic parameters from arterial pulse contour analysis).

Loop diuretics may convert an oliguric state into a nonoliguric one [1–3]. This allows the ICU team to apply more sophisticated and complex pharmacological treatments, as urinary excretion of drugs' metabolites is improved. Moreover, urine flow theoretically flushes out debris (including denuded epithelium) and avoids tubular obstruction and backflow of glomerular filtrate into the renal interstitium [1–3]. Altogether, nonoliguric AKI is associated with better prognosis [1–3].

Nevertheless, the protective properties of loop diuretics on the kidneys are unclear, and the use of diuretics in patients with AKI has been even suggested to be associated with an increase in mortality [6].

21.2 Main Evidence

Several observational studies as well as randomized controlled trials (RCTs) investigated the impact of loop diuretics on survival in different settings, including AKI (Table 21.1). Their results were mostly inconclusive and often conflicting. The observational study by Mehta et al. [8] was the only investigation that reported a significant effect of diuretics on mortality. Among 552 critically ill patients with acute renal failure, these authors found an increased risk of nonrecovery of renal function or death in those receiving diuretics (odds ratio [OR] 1.77, 95 % confidence interval [CI], 1.14–2.76).

However, no difference or a nonsignificant trend toward increased mortality was found by subsequent meta-analyses [9–12]. In 2006, Ho et al. [10] analyzed 9 RCTs including a total of 849 patients with or at risk for AKI [10]. The relative risk (RR) of in-hospital mortality associated with the use of furosemide was 1.11 (95 % CI 0.92–1.33, $p = 0.28$). It was much higher in patients receiving furosemide for prevention (RR 2.33, 95 % CI 0.75–7.25) than in patients treated for established renal failure (RR 1.09, 95 % CI 0.9–1.31). Also Bagshaw et al. [9] found only a nonsignificant trend toward increased mortality in patients receiving loop diuretics (OR 1.28, 95 % CI 0.89–1.84, $p = 0.18$). Sampath et al. [12] summarized 13 studies and found that mortality did not differ between subjects treated with loop diuretics or not (RR 1.10, 95 % CI 0.85–1.42). These results were similar when considering either the eight non-randomized studies (RR 1.09, 95 % CI 0.91–1.25) or the five RCTs (RR 1.12, 95 % CI 0.92–1.35) alone. Finally, in 2010 Ho et al. published an updated review summarizing data on 244 patients at risk for AKI and 632 patients with renal failure [11]. The overall effect on mortality was not significant (RR 1.12, 95 % CI 0.93–1.34), and it slightly differed quantitatively between "prevention" (RR 1.73, 95 % CI 0.62–4.80) and "treatment" group (RR 1.10, 95 %CI 0.92–1.33).

On this basis, the current KDIGO guidelines [13] do not recommend loop diuretics to prevent AKI (class 1B recommendation, i.e., strong recommendation based on moderate-quality evidence), while only a weak recommendation can be made

Table 21.1 Effect of loop diuretics on mortality in non-randomized and randomized trials

Author (year of publication)	Setting	Mortality rate	OR/RR (95 % CI)	*p*	Overall effect on mortality
Non-randomized trials					
Beroniade (1969)	Treatment of RF	LD: 3/12 CTR: 6/12	OR 0.33 (0.06–1.88)	0.21	NONE/NS
Borirakchanyav et al. (1978)	Treatment of RF	LD: 0/6 CTR: 0/8	OR 1.31 (0.02–75.12)	0.9	NONE/NS
Chandra (1975)	Treatment of RF	LD: 5/12 CTR: 3/5	OR 0.48 (0.06–3.99)	0.45	NONE/NS
Mehta (2002)	Treatment of RF	NA	OR 1.68 (1.06–2.64)	NA	INCREASE
Minuth (1976)	Treatment of RF	LD: 47/69 CTR: 12/25	OR 2.31 (0.91–5.89)	0.12	NONE/NS
Uchino (2004)	Treatment of RF	NA	OR 1.22 (0.91–1.6)	NA	NONE/NS
Randomized trials					
Brown (1981)	Treatment of RF	LD: 18/28 CTR: 16/28	RR 1.13 (0.74–1.72) OR 1.35 (0.46–3.96)	0.58	NONE/NS
Canterovich (1973)	Treatment of RF	1st cohort: LD: 15/34 CTR: 7/13	1st cohort: RR= 0.82 (0.44–1.54) OR 0.68 (0.19–2.44)	0.54	NONE/NS
		2nd cohort: LD: 18/39 CTR: 11/19	2nd cohort: RR 0.80 (0.48–1.33) OR 0.62 (0.21–1.89)	0.38	

(continued)

Table 21.1 (continued)

Author (year of publication)	Setting	Mortality rate	OR/RR (95 % CI)	*p*	Overall effect on mortality
Canterovich (2004)	Treatment of AKI	LD: 59/166 CTR: 50/164	RR 1.17 (0.86–1.59) OR 1.26 (0.79–1.99)	0.33	NONE/NS
Grams (2011)	Treatment of AKI (*in ALI*)	NA	OR 0.73 (0.42–1.26)	0.26	NONE/NS
Hager (1996)	Prevention of RF	LD: 6/62 CTR: 3/59	RR 1.90 (0.5–7.26) OR 2.07 (0.49–8.71)	0.35	NONE/NS
Kleinknecht (1976)	Treatment of RF	LD: 13/33 CTR: 12/33	RR 1.08 (0.58–2.01) OR 1.14 (0.42–3.08)	0.8	NONE/NS
Lassnigg (2000)	Prevention of AKI	LD: 4/41 CTR: 1/40	RR 3.90 (0.46–33.42) OR 4.22 (0.45–39.5)	0.21	NONE/NS
Lumlertgul (1989)	Treatment of RF (*in malaria*)	LD: 0/4 CTR: 0/4	RR 1.0 (0.02–41.2) OR 1.0 (0.02–62.3)	1.0	NONE/NS
Mahesh (2008)	Prevention of AKI	LD: 1/21 CTR: 2/21	RR 0.50 (0.05–5.10) OR 0.47 (0.04–5.68)	0.56	NONE/NS
Shilliday (1997)	Treatment of RF	LD: 42/62 CTR: 15/30	RR 1.10 (0.73–1.67) OR 2.10 (0.86–5.12)	0.1	NONE/NS

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Table 21.1 (continued)

Author (year of publication)	Setting	Mortality rate	OR/RR (95 % CI)	*p*	Overall effect on mortality
Van der Voort (2009)	Treatment of AKI	LD: 13/36 CTR: 11/35	RR 1.15 (0.6–2.21) OR 1.23 (0.46–3.31)	0.68	NONE/NS

AKI acute kidney injury, *ALI* acute lung injury, *CTR* control group, *LD* loop diuretic group, *OR* odds ratio, *RR* relative risk, *CI* confidence interval, *NA* nonapplicable, *NS* not significant, *RF* renal failure

against their use in patients with established AKI (class 2C recommendation, i.e., weak recommendation based on low- or very low-quality evidence) [6, 13].

As mentioned, the renal protective role of loop diuretics is controversial. The meta-analysis by Bagshaw et al. [9] found that in patients treated with diuretics, as compared with control, the mean duration of renal replacement therapy (RRT) and the mean time to spontaneous decline in serum creatinine level were reduced by 1.4 ($p=0.02$) and 2.1 days ($p=0.01$), respectively. Moreover, patients receiving diuretics had a 2.6 times greater chance of increase in urine output ($p=0.004$). Conversely, in their two subsequent meta-analyses, Ho et al. [10, 11] showed that furosemide had no effect on RRT need (RR 0.99, 95 % CI 0.8–1.2 [10] and RR 1.02, 95 % CI 0.9–1.06 [11]). Also the number of dialysis sessions required after pharmacological treatment was not significantly affected by furosemide (weighted mean difference −0,48, 95 % CI −1.45–0.50) [10]. Using a Bayesian statistical approach, Sampath et al. [12] confirmed that the oliguric period of acute renal failure was shortened by the use of loop diuretics (mean difference −7.7 days, 95 % CI −12.5 to −2.08), which was also associated with a high probability of a significant reduction in the number of dialysis sessions. However, there was no between-group difference in terms of time to normalization of creatinine/urea concentrations (mean difference −1.54 days, 95 % CI −5.62 to 2.46).

The use of loop diuretics has been even suggested to cause harm to the kidney and be associated with both renal and extrarenal diseases. In a prospective observational study of critically ill patients, Levi et al. [14] identified the use of furosemide as a significant risk factor for AKI (OR 3.27, 95 % CI 1.57–6.80), also after adjustment for age (OR 1.02, 95 % CI 1.00–1.04) and coexistence of sepsis/septic shock (OR 3.12, 95 % CI 1.36–7.14). In the subset of patients with septic shock, the use of furosemide increased the risk of AKI even further (OR 5.5, 95 % CI 1.16–26.02). Wu et al. [15] found that AKI patients treated with furosemide were more likely to have cardiovascular disease (38.9 vs. 18.4 %), arterial hypertension (42.0 vs. 29.2 %), chronic kidney disease CKD (55.0 vs. 27.0 %), and type 2 diabetes mellitus (17.6 vs. 4.3 %) as compared to subjects not treated with diuretics. Interestingly, only in 27.5 % of cases these conditions were solely associated with the use of diuretics, whereas in 29.8 % of cases a combination of diuretics and other nephrotoxic agents (including antibiotics, contrast media, nonsteroidal anti-inflammatory

drugs, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, etc.) was present. The degree of renal injury is believed to be positively correlated with the dose of diuretic [9–12, 15], and the risk of AKI is increased by approximately 64 % when diuretics are combined with nonsteroidal anti-inflammatory drugs (RR 1.64, 95 % CI 1.17–2.29) [16]. The great asset of the study by Wu et al. [15] was the opportunity to look into histopathology results of renal biopsies: 58 out of 63 examined cases showed signs of tubular injury or necrosis, out of which 51 showed vacuolar degeneration of tubular epithelial cell and 27 cases showed tubular basement membrane fracture or exposure.

21.3 Pharmacological Properties

The use of loop diuretics to prevent or treat fluid overload is based on their pharmacological properties to increase urine output. Loop diuretics act on the thick ascending limb of the loop of Henle where they inhibit sodium-potassium-chloride (Na-K-2Cl) cotransporter, causing natriuresis. This leads to reduced osmolality of renal medulla and decreased water reabsorption. The inhibition of active sodium transport reduces both oxygen consumption and oxygen metabolic demand of renal tubules. Furosemide also inhibits the enzyme prostaglandin dehydrogenase and causes renal vasodilation with improved renal blood flow. All these effects can theoretically confer protection against ischemic or nephrotoxic injury by improving renal medullary oxygen balance [1–3, 11], although, as mentioned, loop diuretics are thought to possibly cause renal injury [14–16].

Since loop diuretics are largely excreted unchanged in the urine and influence reabsorption from the luminal site, it is the urinary excretion of the drug, not its plasma concentration, that determines the diuretic efficacy. Because loop diuretics are bound to plasma proteins, the reduction in the protein-bound fraction of furosemide due to hypoalbuminemia or the presence of another highly protein-bound drug (e.g., warfarin, phenytoin) increases its volume of distribution, thereby augmenting its external clearance and decreasing urinary excretion. Albuminuria results in urinary drug binding, decreasing furosemide effectiveness [1–3, 11].

Through their renal action, loop diuretics potentially induce hypovolemia, hypokalemia, hypophosphatemia, hypomagnesemia, and metabolic alkalosis. As a weak organic acid, furosemide acidifies urine and reduces the solubility of myoglobin and hemoglobin in patients with rhabdomyolysis and intravascular hemolysis (e.g., due to cardiopulmonary bypass or intra-aortic balloon pump counterpulsation). Aciduria may also promote free radical formation in the urine caused by contrast media. In patients with reduced renal clearance, high-dose furosemide may cause mostly reversible ototoxicity. High-dose furosemide may also induce systemic vasoconstriction. Finally, loop diuretics promote the reduction of mucociliary transport and sputum clearance by inhibiting Na-K-2Cl cotransporter in the respiratory tract [1–3, 11].

There are several drug interactions that need to be taken into account. Loop diuretics reduce the clearance of theophylline, gentamicin, and other organic acids

Clinical Summary

Drug	Indications	Cautions	Side effects	Dose	Notes
Furosemide	Fluid overload Hyperkalemia Hypercalcemia	Preload must be carefully preserved Serum potassium should be closely monitored	Polyuria, hypokalemia, hypophosphatemia, hypomagnesemia, aciduria, metabolic alkalosis, ototoxicity (hearing loss, deafness or tinnitus) with large doses, vertigo, seizures, allergic reactions, agranulocytosis	40–80 mg orally (maximum 600 mg/day) in adults 1–3 mg/kg/day orally in children Continuous/bolus i.v. infusion: initial bolus dose (usually 0.1 mg/kg/h), then adjusted according to the clinical response (usually 0.1–0.5 mg/kg/h)	According to the available evidence, only a weak recommendation can be made to avoid loop diuretics in order to reduce mortality in patients with AKI

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Drug	Indications	Cautions	Side effects	Dose	Notes
Torasemide	Congestive heart failure	Maintain electrolytes during treatment	As above	5 mg (up to 20 mg) i.v./orally per day maximum single dose 200 mg	The putative mechanism of increased mortality is unclear, but may involve low cardiac output/hypotension and/or direct renal injury
Bumetanide	Ascites Peripheral edema Pulmonary edema		As above	0.5–2 mg orally once daily 0.5–1 mg once daily (i.v., im) Continuous i.v. infusion: 1 mg/h (up to 12 mg/day)	
Ethacrynic acid	Ascites Peripheral edema Pulmonary edema 40–80 mg orally (maximum 600 mg/day) in adults		As above	50 mg orally once daily 50 mg i.v. once daily	

(e.g., benzylpenicillin, cephalosporins, oxypurinol, active metabolite of oseltamivir), increase the risk of amphotericin-induced hypokalemia, the antiepileptic effect of valproate, the hypotensive effect of angiotensin-converting enzyme (ACE) inhibitors, and reduce the therapeutic effect of warfarin [11].

21.4 Therapeutic Use

The most popular loop diuretic in clinical use is furosemide (frusemide), and most clinical trials used this drug in the treatment arm [1]. Other loop diuretics available on the market include torasemide (torsemide), bumetanide, and ethacrynic acid.

Furosemide is approved to be used to treat edema in the course of congestive heart failure (CHF), liver cirrhosis, and renal failure and in treatment of arterial hypertension mainly as part of a multidrug regimen [17, 18]. The recommended dose is 40–80 mg per day orally (maximum 600 mg/day) in adults and 1–3 mg kg^{-1} day^{-1} orally in children. The intravenous dose is approximately 0.1 mg kg^{-1} h^{-1}. However, the dose is usually adjusted according to the clinical response. A small dose of furosemide (i.e., <10 mg) can be considered to correct hyperchloremic acidosis induced by a large amount of 0.9 % saline infusion in patients who are not hypovolemic [11]. If intravenous furosemide is used to replace oral furosemide, one half of the oral dose is required. In fact, i.v. furosemide is about twice as potent and rapid than oral furosemide in inducing diuresis [11].

Torasemide is approved to be used to prevent or treat edema in the course of CHF [17, 18]. Its starting dose is 5 mg/day (up to 20 mg/day) given orally or i.v. (maximum single dose 200 mg). Bumetanide and ethacrynic acid are used for ascites, edema, and pulmonary edema [17, 18]. Bumetanide is given once daily at dose of 0.5–2 mg orally or 0.5–1 mg by i.v. or intramuscular injection. Continuous i.v. infusion is usually 1 mg/h (up to 12 mg/day). The dose of ethacrynic acid is 50 mg (orally or i.v.) once daily.

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