Kidney & Blood Pressure Research

Kidney Blood Press Res 2019;44:457–464
DOI: 10.1159/000501315
Received: March 5, 2019
Accepted: June 3, 2019
Published online: July 30, 2019

Review Article

Loop Diuretics in Acute Kidney Injury Prevention, Therapy, and Risk Stratification

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Keywords
Loop diuretics · Acute kidney injury · Prevention · Therapy · Risk stratification

Abstract
Background: Loop diuretics (LD) are widely used in emergency and intensive care medicine. ***Summary:*** The substances increase the clearance of electrolytes and water; thus, they allow us to control hypervolemia and to prevent patients from pulmonary edema. LD are also frequently applied to patients with an acute decrease in glomerular filtration rate, namely, acute kidney injury (AKI). Nevertheless, volume depletion may be associated with reduced renal perfusion and possibly slower restitution or even aggravation of kidney dysfunction. Several trials on the preventive or therapeutic efficacy of LD have been published since the early 1970s. Our review article is intended to summarize the most important references related to this topic. In addition, we discuss the diagnostic value of the so-called furosemide stress test. The currently available data indicate that LD may act in a beneficial manner as long as euvolemia is maintained (matched hydration). ***Key Massages:*** LD are not beneficial for AKI treatment if kidney-related endpoints are considered. In certain situations, AKI prevention with LD can be associated with favorable outcomes as long as euvolemia is maintained. LD can help to identify AKI subjects at a higher risk of AKI progression, but the exact clinical consequences need to be determined.

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Introduction

Acute kidney injury (AKI) affects increasing numbers of patients worldwide. In Continental Europe, it was estimated that approximately 15% of all subjects treated in hospitals develop an acute decline in kidney function during the course of their disease [1]. Particularly high incidence rates are found in ICU, and the prognosis remains poor. AKI has been identified as an independent risk factor for mortality in patients undergoing intensive care therapy [2, 3]. AKI treatment focuses on the avoidance of further organ damage, but specific measures are missing in most situations.

Loop diuretics (LD) – for instance, furosemide – are used intensively in emergency and intensive care medicine, since they offer the possibility of eliminating large amounts of electrolytes and water as long as the kidneys are capable to filtrate. Thus, hyperhydration may be controlled. However, reduced glomerular filtration characterizes AKI of various etiologies. Although LD are frequently used if fluid retention results from impaired kidney function, it remains debatable whether the renal prognosis per se can be improved by the drugs or not. In theory, LD increase the tubular flow of filtrate and thus reduce tubular obstruction. In addition, by inhibiting tubular electrolyte reuptake, they decrease the medullary net oxygen consumption. Finally, the drugs have been reported to even modulate tubular cell survival in a beneficial manner [4]. On the other hand, LD administration results in volume depletion and possibly renal hypoperfusion. Kidney function may decrease even further.

In the past, several trials investigated the use of LD for AKI prevention and therapy. Our review article is intended to discuss the most important investigations related to this topic. It is divided into four sections. The first section discusses pharmacodynamic aspects, the second and third sections summarize the systematic data on LD in AKI prevention and therapy, and the last section is dedicated to the so-called furosemide stress test (FST). Before we continue, it needs to be mentioned that studies on either AKI prevention or AKI therapy using LD can be compared only in a limited manner. Our understanding of AKI pathophysiology and outcomes has significantly changed over time; the same applies to the exact definition of the syndrome. For instance, since 2004 at least four AKI definitions have been proposed [5]: the RIFLE and the AKIN criteria, the criteria by Waikar and Bonventre, and the definition by KDIGO published in 2012 [6–9]. Earlier concepts – for instance, as published by Hou et al. [10] in 1983 – employed two parameters: the baseline creatinine value and its relative increase over time. Other definitions have been developed as well. Thus, particularly older investigations, published before the mid 2000s, should always be assessed in a critical manner.

Pharmacodynamics of LD

LD are drugs with a high degree of plasma protein binding, the most important binding partner being albumin [11]. Thus, situations with lower availability of albumin may decrease the effectiveness of LD therapy. After having been secreted into the proximal convoluted tubule, LD decrease the activity of the sodium-potassium-chloride cotransporter located within the apical membranes of tubular epithelial cells in the thick ascending loop of Henle [12]. If glomerular filtration stops, LD are completely ineffective, which explains why anuric patients do not benefit from the substances at all. LD act from the luminal site in a reversible manner. The cotransporter function critically depends on the availability of an energy-supplying substrate, namely, adenosine triphosphate. Thus, the net oxygen consumption of the kidney decreases. Reduced ion reabsorption results in increased tubular filtrate flow, followed by increased volume clearance. In theory, both effects, reduced adenosine triphos-

phate utilization and increased tubular flow, are beneficial in situations in which the function or even the structure of the kidney is compromised. Another effect of these drugs (e.g., furosemide) – potentially advantageous in evolving pulmonary edema – is venodilation [13], followed by reduced blood flow to the heart.

Besides their substantial effects on renal electrolyte and water clearance, LD have been shown to modulate cell survival and to influence the angiogenic balance. In an experimental study, Aravindan et al. [4] suggested antiapoptotic effects of LD in a rat model of ischemia-reperfusion injury. Earlier, the same group had shown attenuation of ischemia-reperfusion injury-induced suppression of angiogenesis-related genes by LD [14]. Finally, a study performed on isolated rat kidneys indicated protective effects of LD on the S3 segment (a certain tubular section) [15].

The rationale for LD administration in evolving or established AKI is to increase the tubular flow of filtrate and to reduce net nutrient and thus oxygen consumption. On the other hand, LD-induced volume depletion may potentially induce or aggravate renal hypoperfusion and perpetuate AKI.

AKI Prevention

In a meta-analysis published in 2010, Ho and Power [12] reviewed several trials that investigated the preventive or therapeutic role of LD in AKI. Although the authors concluded that the drugs most likely do not improve renal function (or mortality) in a direct manner, some trials shall be outlined briefly. In general, we were interested in studies that compared LD therapy with no diuretic intervention at all.

Solomon et al. [16] evaluated chronic kidney disease (CKD) subjects (mean ± SD serum creatinine concentration 186 ± 53 μmol/L) undergoing cardiac angiography. The patients either received saline alone or saline combined with LD or mannitol. The largest decline in kidney function was observed when saline and LD were administered in combination. In a randomized, double-blind, placebo-controlled trial, Hager et al. [17] compared continuous furosemide infusion with no LD administration in post-surgery patients and did not detect any differences in glomerular filtration rate reduction between the two groups. However, hypokalemia occurred more frequently in the treatment group.

In 2000, Lassnigg et al. [18] reported outcomes of elective cardiac surgery subjects receiving either isotonic sodium chloride or dopamine (2 μg/kg/min) or furosemide (0.5 μg/kg/min). Post-surgery creatinine levels showed the highest increase in the LD group. Finally, Mahesh et al. [19] investigated post-cardiac surgery patients at a higher AKI risk (preoperative creatinine <130 μmol/L) who received furosemide (4 mg/kg) or saline (2 mL/h) until hour 12 after surgery. Even though urine output was significantly higher in the treatment group, the incidence of renal dysfunction did not differ in a significant manner. According to these studies, LD administration was by no means associated with any AKI risk reduction, to say the least.

Some newer studies, which were also mentioned in a recent article by Bove at al. [20], shall be addressed as well. Dussol et al. [21] evaluated the incidence of contrast-induced nephropathy (CIN) in CKD subjects (mean serum creatinine 201 ± 81 μmol/L) undergoing preventive care with either oral or i.v. saline (± theophylline or furosemide). CIN occurred at comparable rates in the respective groups, indicating that the LD were unable to improve renal prognosis after contrast medium administration. Another CIN-related trial compared i.v. hydration alone with hydration plus LD (single dose injection 20 mg). Treatment was initiated after coronary angiography/angioplasty. The LD group displayed lower postsurgical increases in serum creatinine, indicating protective effects of additional LD therapy [22]. The

MYTHOS trial [23] confirmed the beneficial effects of LD in subjects receiving contrast medium. CKD patients were infused with saline alone or were treated with both saline and furosemide (0.5 mg/kg bolus furosemide with matched hydration; FMH group); 4.6% in the FMH group, versus 18% in the control group, developed CIN ($p = 0.005$). Finally, the aim of the AKIGUARD (Acute Kidney Injury GUARding Device) trial was to compare CIN incidence rates among CKD subjects treated with sodium bicarbonate/isotonic saline/N-acetylcysteine/vitamin C (BS-NAC) in comparison with a 250-mL isotonic saline bolus, followed by a 0.5 mg/kg furosemide i.v. bolus (matched hydration group [MHG]) [24]. The CIN incidence was 7% (MHG) versus 25% (BS-NAC group) ($p = 0.01$).

Particularly the last two studies indicate a promising concept in CIN: matched hydration. Recently, Putzu et al. [25] published a meta-analysis in which four studies were included. Two of these have been discussed above. The authors concluded that combined administration of fluid and LD may potentially serve as a strategy for CIN prevention in the future. In a commentary on Putzu's article published in 2017, Bartorelli and Marenzi [26] emphasized the fact that the volume must be applied in a very balanced or matched manner if LD should act protectively. This may be achieved using devices such as the RenalGuard® System, an automated fluid-injecting machine that permanently evaluates urine output and adapts the volume to be infused accordingly in order to maintain euvolemia. Three further studies confirmed the effectiveness of the RenalGuard® System [27–29], and a randomized controlled trial has been initiated [30].

This section may be closed with the following conclusion. In terms of AKI prevention, LD may act protectively in certain situations (contrast medium administration) as long as the drugs do not significantly decrease the intravascular volume and thus renal perfusion. Matched hydration is most likely associated with increased tubular flow of filtrate without whole-body volume depletion and without renal malperfusion. However, additional randomized trials are necessary before the concept of "diuresis while maintaining euvolemia" (matched hydration) can be recommended in general [30].

AKI Therapy

This section starts with the discussion of several studies that were partially mentioned by Ho and Power in 2010 [12]. A very early trial (from 1973) was performed on 105 patients suffering from established AKI [31]. Although somehow irritating compared to the usual doses applied today, the subjects received daily injections of 2 g of furosemide. This treatment improved diuresis and thereby shortened the duration of oliguria. In addition, the mean number of dialyses was lower in the treatment group. The authors concluded that high doses of the drug may potentially act beneficially. In the following year, Ganeval and colleagues commented on the study [32] and discussed several limitations, most importantly the lack of detailed information about the control and treatment groups.

In 1976, Kleinknecht et al. [33] reported on the use of furosemide in 33 subjects with established oliguric AKI. The drug was administered every 4 h, and the dosage ranged from 1.5 to 6.0 mg/kg. The authors did not find any differences in renal outcome parameters in comparison to a control group of equal size. In a prospective, placebo-controlled study, Shilliday et al. [34] evaluated the following protocol in 92 AKI patients: dopamine + mannitol + either furosemide or torasemide or placebo. The diuretics were applied at 3 mg/kg. Although the LD-treated subjects showed higher urine output and the nonoliguric patients had a lower risk of mortality, the overall outcomes did not differ between the LD-treated and the LD-naïve individuals. The lower mortality among the nonoliguric subjects most likely resulted from the lower overall morbidity in this particular group. A prospective, placebo-controlled trial published in 2009 [35] compared furosemide (0.5 mg/kg/h) with continuous saline infusion

Table 1. Preventive or therapeutic role of LD in evolving or established AKI

Reference	Design	Result and outcome
Prevention		
Dussol et al. [21]	Prospective, randomized; low-osmolality contrast agent in subjects with pre-existing CKD – Cockcroft clearance of 37±12 mL/min/1.73 m^2; *n* = 312; oral or i.v. saline (± theophylline or furosemide)	Comparable CIN incidence in all three groups – LD neither advantageous nor disadvantageous (↔)
Gu et al. [22]	Prospective, randomized; coronary angiography; *n* = 859; i.v. furosemide vs. no intervention immediately after angiography	Lower postsurgical increases in serum creatinine after LD administration – LD advantageous (+)
Hager et al. [17]	Randomized, double-blinded, placebo-controlled; ICU subjects undergoing major abdominal, chest, or vascular surgery; *n* = 121; furosemide vs. placebo	No differences in GFR reduction between the two groups – LD neither advantageous nor disadvantageous (↔)
Mahesh et al. [19]	Randomized, double-blinded, placebo-controlled; coronary artery bypass surgery; preoperative serum creatinine >130 µmol/L; *n* = 42; furosemide vs. saline, start after induction of anesthesia	Incidence of renal dysfunction not different between the two groups – LD neither advantageous nor disadvantageous (↔)
Bartorelli and Marenzi [26]	Prospective, randomized; coronary procedures; *n* = 170; i.v. furosemide + saline (matched hydration, FMH) vs. saline	4.6% in the FMH vs. 18% in the control (saline) group developed CIN ($p = 0.005$) – LD advantageous (+)
Solomon et al. [16]	Prospective, randomized; coronary angiography; pre-existing CKD – serum creatinine 186±53 µmol/L; *n* = 78; saline vs. saline + furosemide vs. saline + mannitol	Lowest rise in serum creatinine in subjects receiving saline alone – LD disadvantageous (–)
Usmiani et al. [24]	Prospective, randomized; coronary procedures; pre-existing CKD – eGFR <60 mL/min/1.73 m^2; *n* = 130; bicarbonate/isotonic saline/N-acetylcysteine/vitamin C vs. matched hydration	Significantly lower CIN incidence after matched hydration – LD advantageous (+)
Treatment		
Cantarovich et al. [31]	Retrospective; established oliguric AKI; *n* = 105; furosemide with 2 g daily vs. no LD	Improved diuresis and shorter duration of oliguria – LD advantageous (+)
Kleinknecht et al. [33]	Prospective, randomized; established oliguric AKI; *n* = 66; furosemide vs. no LD	Differences in renal outcome parameters – LD neither advantageous nor disadvantageous (↔)
Shilliday et al. [34]	Prospective, randomized, placebo-controlled, double-blinded; established AKI; *n* = 92; dopamine + mannitol + either furosemide or torasemide or placebo	No differences in renal outcome parameters – LD neither advantageous nor disadvantageous (↔)
van der Voort et al. [35]	Prospective, randomized, placebo-controlled, double-blinded; AKI subjects in continuous dialysis; *n* = 71; furosemide vs. placebo, start at the end of dialysis	Higher urinary sodium excretion under LD administration, but no differences in renal outcome parameters – LD neither advantageous nor disadvantageous (↔)

Three trials showed beneficial effects in AKI prevention, and one study (published in 1973 [31]) indicated substantial therapeutic effects. Details on the studies are discussed in the main text. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; LD, loop diuretics; CIN, contrast-induced nephropathy.

in patients after completion of continuous venovenous hemofiltration at the ICU. The subjects in the treatment group showed higher urine volumes and higher urinary sodium excretion, but they did not differ in terms of renal outcome parameters. Lately, Bove et al. [20] extensively reviewed the data on preventive and therapeutic LD administration, but the focus was on intermittent versus continuous drug delivery (Table 1).

Taken together, the data so far available from controlled trials do not support the idea of LD as reliable AKI therapeutics.

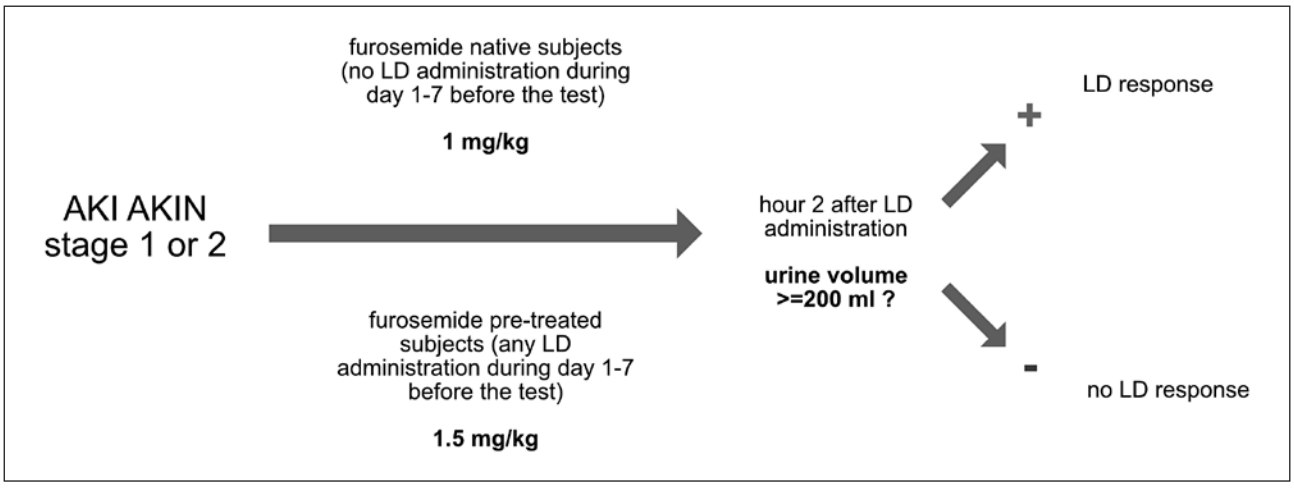

Fig. 1. Furosemide stress test. The dosage of the drugs depends on whether subjects have received LD previously (day 1–7 before testing). Urine output must be quantified until the next two hours after drug administration. A total volume of 200 mL or more (100 mL/h) indicates LD responsiveness [36].

Furosemide Stress Test

The FST was designed to estimate AKI progression risk. As pointed out by Chawla et al. [36], the question "When should renal replacement therapy (RRT) be initiated?" was identified as one of the most important AKI-related questions in daily clinical medicine. In an article published in 2013, the authors reported on two cohorts, with the first (n = 23) analyzed in a retrospective manner and the second (n = 54) analyzed prospectively. All participants were critically ill and suffered from early AKI. The subjects received furosemide once (1 or 1.5 mg/kg), and the primary endpoint was the development of AKI of AKIN stage 3 [37]. The cutoff for predicting AKIN stage 3 was a urine output <100 mL/h during the next 2 h after LD administration [36].

In a review article published in 2016, it was emphasized that subjects undergoing the FST must be euvolemic in order to guarantee its safety and validity [38]. Every net volume loss should be replaced. In a more recently published retrospective analysis, Matsuura et al. [39] analyzed the combined prognostic value of a furosemide bolus (at variable doses) and plasma neutrophil gelatinase-associated lipocalin (NGAL). Only subjects with furosemide responsiveness and without continuous LD infusion were included. Patients with AKI of AKIN stage 3 were excluded as well. Only 1 subject with a plasma NGAL level <142 ng/mL progressed to AKIN stage 3. In those individuals with plasma NGAL levels >142 ng/mL, furosemide responsiveness was associated with an AUC of 0.84 for AKI progression. It was concluded that the diagnostic value of the FST could be improved by simultaneous biomarker stratification.

Recently, Lumlertgul et al. [40] prospectively compared early (hours 0–6) with late initiation of RRT in FST-responsive patients, but they failed to show any differences in 28-day mortality, fluid balance at day 7, and persistent RRT dependency at day 28. In a very recent study, Udomkarnjananun et al. [41] evaluated the diagnostic value of the FST in kidney transplant recipients. The test allowed to identify subjects with an increased risk of delayed graft function (87.5% sensitivity, 82.9% specificity, and 82.5% accuracy) (Table 1).

Taken together, the FST has been shown to be a useful tool for the identification of AKI subjects at a higher risk of disease progression. It needs to be evaluated which therapeutic consequences may result from this, particularly for critically ill patients in the ICU. Figure 1

summarizes the approach to patients intended to undergo the FST, including dosing recommendations. It emphasizes the fact that dosage depends on whether or not a patient has previously been treated with LD.

Conclusions and Recommendations

Regarding the currently available data from clinical trials, three conclusions may be drawn:

- LD are not beneficial for AKI treatment if kidney-related endpoints are considered
- In certain situations, AKI prevention by LD can be associated with favorable outcomes as long as euvolemia is maintained
- LD can help to identify AKI subjects at a higher risk of AKI progression, but the exact clinical consequences need to be determined

Disclosure Statement

The authors declare no conflicts of interest.

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