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REVIEW ARTICLE

Benefits and risks of furosemide in acute kidney injury

K. M. Ho[1] and B. M. Power[2]

1 Intensive Care Specialist, Royal Perth Hospital and Clinical Associate Professor, University of Western Australia, Perth, WA, Australia
2 Intensive Care Specialist, Joondalup Hospital, Perth, WA, Australia

Summary

Furosemide, a potent loop diuretic, is frequently used in different stages of acute kidney injury, but its clinical roles remain uncertain. This review summarises the pharmacology of furosemide, its potential uses and side effects, and the evidence of its efficacy. Furosemide is actively secreted by the proximal tubules into the urine before reaching its site of action at the ascending limb of loop of Henle. It is the urinary concentrations of furosemide that determine its diuretic effect. The severity of acute kidney injury has a significant effect on the diuretic response to furosemide; a good 'urinary response' may be considered as a 'proxy' for having some residual renal function. The current evidence does not suggest that furosemide can reduce mortality in patients with acute kidney injury. In patients with acute lung injury without haemodynamic instability, furosemide may be useful in achieving fluid balance to facilitate mechanical ventilation according to the lung-protective ventilation strategy.

Correspondence to: Kwok M. Ho
E-mail: kwok.ho@health.wa.gov.au
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Acute kidney injury (AKI) is a serious medical condition with significant mortality and morbidity [1]. The causes of AKI include infection, hypovolaemia, cardiac insufficiency, and nephrotoxins such as aminoglycoside antibiotics and radiocontrast agents. Despite advances in techniques and technologies in renal replacement therapy, mortality associated with AKI has remained largely unchanged over the past decade [2].

Non-oliguric AKI is well known to be associated with a better prognosis than oliguric AKI [3], and as such, non-oliguric AKI is classified separately from oliguric AKI according to the AKI RIFLE (Risk, Injury, Failure, Loss, and End-stage) criteria suggested by the Acute Dialysis Quality Initiative (ADQI) group [4]. Because oliguria is a risk factor or marker of poor outcomes in AKI and also makes fluid and electrolyte management more difficult, many clinicians use high doses of intravenous furosemide to increase urine output or in an attempt to convert oliguric to non-oliguric AKI. Although furosemide is widely used in different stages of AKI, its clinical roles and effectiveness remain uncertain and controversial [5–15].

Randomised controlled trials are of pivotal importance in guiding clinicians' daily practice, but pharmacological principles, experimental data, and clinical observations are also important [16], especially when the evidence from randomised controlled trials is inconclusive. This narrative review aims to provide an update on the potential roles of furosemide in AKI by summarising its pharmacological properties, side effects, and evidence of effectiveness from randomised controlled trials.

During the literature search for relevant articles in MEDLINE and EMBASE databases before 20 November 2009, the following search terms, 'acute renal failure', 'acute kidney injury', 'dialysis', 'renal replacement therapy', 'tumour lysis syndrome', 'hypercalcaemia', 'haemoglobinuria', 'contrast', 'drug interaction', 'side effects', 'prevention', 'prognosis', or 'therapy' with 'furosemide' were used without any language restrictions. Relevant references from the articles identified from the literature search were also retrieved for further analysis.

In the review on pharmacological properties of furosemide, both animal and human data were used without pooling the data by quantitative methods. As for the assessment of effectiveness of furosemide, only randomised controlled trials comparing furosemide with a placebo to prevent or treat AKI published before 20

November 2009 were included. We updated the results of our previous meta-analysis [17], using the same study inclusion and exclusion criteria and methodology. In this review only the effect of furosemide on the risk of requiring renal replacement therapy and mortality was analysed.

Pharmacology of furosemide

Furosemide is a weak organic acid. It is predominantly cleared by the kidneys (85%) in which about half is metabolised, and half is actively secreted in an unchanged form [18] by the organic acid transporters in the proximal tubules (Fig. 1). The normal systemic clearance of furosemide is about 19 $ml.kg^{-1}.min^{-1}$ (Table 1) [18].

Furosemide is highly protein bound (> 98%) and only a very small fraction of the drug can be filtered through the glomerulus [19]. The binding of furosemide to plasma proteins facilitates its renal tubular secretion and diuretic effect [20]. A reduction in the protein-bound fraction of furosemide in hypoalbuminaemia or in the presence of another highly protein-bound drug (e.g. warfarin, phenytoin) reduces the tubular secretion of furosemide and its diuretic effect [20–22], and at the same time increases its metabolic clearance. Hence, the presence of a highly protein-bound drug and hypoalbuminaemia can both contribute to resistance to the diuretic effect of furosemide. These experimental findings are supported by the clinical observation of an enhanced diuretic response to furosemide when concomitant albumin administration is used in patients with hypoproteinaemia [23].

Furosemide acts on the sodium-chloride-potassium [Na-K-Cl_2] co-transporters at the intra-luminal side of the ascending limb of the loop of Henle (Fig. 1). The accumulation of ions inside the lumen of renal tubules after administration of furosemide inhibits the passive re-absorption of potassium, calcium and magnesium, resulting in increased urinary losses of these ions. Furosemide has also been shown to block the tubulo-glomerular feedback response [24]. There are three determinants of diuretic response to furosemide: the urinary concentrations of furosemide; the time of delivery of furosemide to the site of action; and the dynamics of the response at the site of action [19]. The urinary concentration of furosemide can be reduced in the presence of other organic acids that compete for the organic

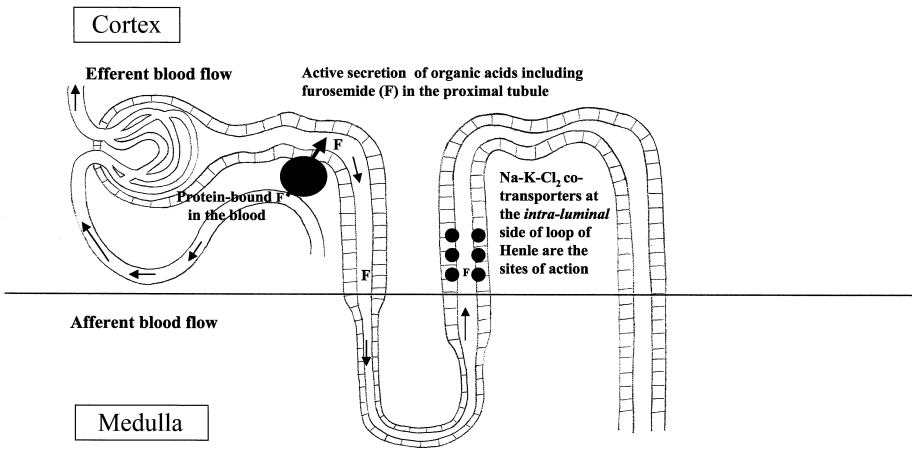

Figure 1 Delivery of furosemide by the proximal tubule to its site of action at the loop of Henle.

Table 1 Pharmacology of furosemide.

An organic acid secreted by organic acid transporters in the proximal tubules into the urine
Clearance = 19 $ml.kg^{-1}.min^{-1}$, 85% cleared by the kidneys
50% metabolised and 50% excreted unchanged by the kidney
The secretion of furosemide by the proximal tubules can be reduced in the presence of other organic acids in the blood
Highly protein-bound (>98%)
Reducing protein binding of furosemide by hypoalbuminaemia or another highly protein bound drug can increase its metabolic clearance, reduce its tubular secretion and diuretic effect
Elimination half-life is about 1.5–2 h in healthy individuals but significantly prolonged in patients with renal failure
The site of action of furosemide is Na-K-Cl_2 co-transporter at the intra-luminal side of the ascending loop of Henle. The diuretic response to furosemide depends on urinary concentrations of furosemide, the time of delivery of furosemide to its site of action, and the dynamics of the response at the loop of Henle

acid transporters in the proximal tubules [19]. The possible competing organic acids may include uraemic acid in renal failure [19] and drugs such as probenecid, benzylpenicillin, cephalosporins, ciprofloxacin, oxypurinol, bumetanide, and active metabolites of oseltamivir [25].

The time course of the delivery of furosemide to its site of action may be affected by cardiac output [26], renal blood flow [27], and the route of furosemide administration. Furosemide infusion is, in general, more effective than boluses in inducing diuresis [28, 29], even in patients with hypoalbuminaemia [30]. The amount of furosemide secreted into the urine appears to be similar after either an intravenous bolus or infusion [19], and as such, the mechanism for the enhanced diuretic action of furosemide infusion may be related to its prolonged inhibition of Na-K-Cl_2 co-transporters.

In terms of dynamics of response, activation of the renin-angiotensin-aldosterone system by dehydration [30], concomitant non-steroidal anti-inflammatory drug (NSAID) treatment, and congestive heart failure are important factors in reducing the pharmacodynamic response to furosemide [19, 26]. For example, intravenous hydration can improve the diuretic response to furosemide, especially when furosemide is given by a bolus instead of an infusion [30].

In patients with AKI, a reduced diuretic response to furosemide may due to a combination of different mechanisms, including reduced tubular secretion of furosemide and a blunted response of the Na-K-Cl_2 co-transporters at the loop of Henle [19]. The diuretic response to furosemide appears to have a significant inverse relationship to the severity of AKI [31].

Current evidence on effectiveness of furosemide from randomised controlled studies

Two randomised controlled studies on the use of furosemide to prevent or treat AKI have been published since the publication of our last meta-analysis [14, 15]. Including the nine studies in our previous meta-analysis [17], a total of 11 studies involving 962 patients were considered in this review [5–15]. The characteristics of the studies are described in Table 2.

Furosemide did not appear to reduce the risk of requiring renal replacement therapy (relative risk (RR) 1.02, 95% CI 0.90–1.16, p = 0.73) and hospital mortality (RR 1.12, 95%CI 0.93–1.34, p = 0.23) when used as a preventive or therapeutic drug in patients at risk of or with established AKI, respectively (Figs 2 and 3). Using all-cause mortality as an end-point, the funnel plot does not suggest the presence of publication bias (Fig. 4). These results confirmed the findings of our previous meta-analysis [17].

The sample size of this meta-analysis has, however, only a power of 80% to detect a 9% reduction in risk of requiring renal replacement therapy if the baseline risk of requiring renal replacement therapy is 40%. There was also some heterogeneity on the effectiveness of furosemide in reducing the risk of renal replacement therapy among the therapeutic trials. As such, it is still possible that furosemide is more useful than placebo in reducing risk of renal replacement therapy, but the current evidence is underpowered to demonstrate such a benefit.

Potential roles of furosemide in patients at risk of AKI

If there are strong experimental data to support the benefits of furosemide in AKI, then a large randomised controlled trial is essential to confirm its effectiveness. Oxygen tension in the renal medulla is comparatively low because only 10% of the renal blood flow goes to the inner medulla [32, 33]. Medullary haematocrit is also low relative to arterial blood [33] and coupled with the relatively high metabolic demand of the loop of Henle, this part of the renal tubules is particularly prone to ischaemia when there is a reduction in renal blood flow. In experimental studies on the *isolated* perfused kidney, furosemide has been shown to reduce renal medullary injury during hypoxic conditions [34–36]. Furosemide may improve the oxygen supply and demand balance by inhibiting Na-K-Cl_2 co-transporter activity and increasing prostaglandin production and blood flow [37, 38]. However, this protective intrarenal haemodynamic response to furosemide is absent if the patient is dehydrated or treated with prostaglandin inhibitors (e.g. NSAIDs) [37], suggesting that dehydration and NSAIDs may counteract the diuretic response to furosemide and any protective effect of furosemide on medullary ischaemia [39]. Furthermore, furosemide has also been shown to impair the glomerular filtration and renal blood flow autoregulation mechanism, making the assumption that inhibition of the Na-K-Cl_2 co-transporters will improve renal tubular oxygenation more uncertain [40].

More recent experimental evidence suggests that the pathogenesis of AKI is far more complicated than a simple hypoxic model, involving inter-related mechanisms of ischaemia, toxins, coagulation, inflammation, and neutrophil-endothelial interactions [41, 42]. The complex pathogenesis of AKI is also supported by the fact that AKI is often only part of a multi-system disease. While AKI may have a significant attributable mortality, it is unusual for AKI per se to be the cause of death [43, 44]. It is thus unrealistic to expect that inhibition of the Na-K-Cl_2 co-transporters alone would have a significant impact on mortality from AKI [17, 45, 46].

Table 2 Characteristics of the included studies.

Study [reference]	Participants	Interventions	Outcomes	Allocation concealment, blinding, % loss to follow up, intention to treat analysis, and Jadad's scale (ranges between 0 and 5)
Lassnigg [5]	126 adult patients with serum creatinine value < 177 μmol.l^{-1} who underwent elective cardiac surgery	Control group (n = 40): 2.5 ml.h^{-1} of 0.9% saline infusion Furosemide group (n = 41): 2.5 mg.h^{-1} of furosemide infusion Study drug started after induction of anaesthesia until 48 h after surgery or discharge from intensive care unit (ICU) The third study group, dopamine infusion (n = 42), was not included in this meta-analysis	Mortality and proportion of patients requiring dialysis	Adequate allocation concealment, double blinded, 2.4% of patients could not complete the study, analysis not by intention to treat 5
Hager [6]	121 patients who underwent major abdominal, chest or vascular surgery, mean serum creatinine concentrations before surgery were 93–105 μmol.l^{-1}	Control group (n = 59): 1.4 ml.h^{-1} of 5% dextrose Furosemide group (n = 62): 1 mg.h^{-1} of furosemide infusion Study drug started after admission to ICU and continued until discharge	Mortality and proportion of patients requiring dialysis	Adequate allocation concealment, double-blinded, blinding, loss to follow-up not reported, analysis by intention to treat not sure 4
Solomon [7]	78 patients with chronic renal insufficiency (serum creatinine > 140 μmol.l^{-1}) who underwent cardiac angiography, mean serum creatinine concentrations of both groups before angiography were 186 μmol.l^{-1}	Control group (n = 28): 0.45% saline 1 ml.kg^{-1}.h^{-1} beginning 12 h before angiography and continued 12 h after angiography Furosemide group (n = 25): 0.45% saline 1 ml.kg^{-1}.h^{-1} beginning 12 h before angiography and continued until 12 h after angiography + 80 mg furosemide intravenously 30 min before angiography The third study group, mannitol with 0.45% saline (n = 25), was not included in this meta-analysis	Proportion of patients requiring dialysis	Adequate allocation concealment, unsure blinding, loss to follow-up not reported, analysis by intention to treat not sure 2
Shilliday [8]	96 patients with acute kidney injury (serum creatinine > 180 μmol.l^{-1} and mean creatinine clearance 7–8 ml.min^{-1}) not due to pre-renal or post-renal causes who had not received furosemide in the preceding 48 h	Control group (n = 30): placebo (not defined) as an iv infusion over 1 h 6 hourly to 21 days Furosemide group (n = 32): iv 3 mg.kg^{-1} 6 hourly reduced to 2 mg.kg^{-1}, then 1 mg.kg^{-1} (if the serum creatinine fell) and stopped when renal function recovered All patients in the study also received dopamine (2 μg.kg^{-1}.min^{-1}) and mannitol 20% 100 ml 6 hourly. The mannitol was stopped on day 3 if the patient remained oliguric. The third study group, torasemide (n = 30), was not included in this meta-analysis	Mortality and proportion of patients requiring dialysis	Allocation concealment unclear, double blinded, 4.2% loss to follow-up, analysis not by intention to treat 3
Kleinknecht [13]	66 patients who had oliguric acute kidney injury (< 500 ml.day^{-1}) but without chronic renal failure	Control group (n = 33): placebo (not defined) Furosemide group (n = 33): 3 mg.kg^{-1} 4 hourly to maintain urine output between 20 to 100 ml.h^{-1} and 6 mg.kg^{-1} if diuresis remained below 20 ml.h^{-1}, 1.5 mg.kg^{-1} if diuresis between 100–150 ml.h^{-1} and no furosemide if diuresis > 150 ml.h^{-1}. The maximum daily dose was 1200 mg. Urine output replaced by 5% dextrose with 6 g.l^{-1} NaCl and 1.5 g.l^{-1} KCl	Mortality and proportion of patients requiring dialysis	Allocation concealment and blinding not clear, loss to follow-up not reported, analysis by intention to treat not sure 1

Table 2 (*Continued*)

Study [reference]	Participants	Interventions	Outcomes	Allocation concealment, blinding, % loss to follow up, intention to treat analysis, & Jadad's scale (ranges between 0 and 5)
Cantarovich [10]	338 patients who had acute kidney injury (plasma urea> 30 mmol.l^{-1} and oligo-anuric for 48 h) and required renal replacement therapy	Control group (n = 164): matched placebo (details not defined) Furosemide group (n = 166): iv 25 mg.kg^{-1} per day infusion, changed to oral 35 mg.kg^{-1}.day^{-1} when tolerated. All drugs given after dialysis if intermittent dialysis was used. Weaned to 20 mg.kg^{-1}.day^{-1} orally or 15 mg.kg^{-1}.day^{-1} iv then 10 mg.kg^{-1}.day^{-1} both orally and iv and then 5 mg.kg^{-1}.day^{-1} before discontinuation when renal function recovered	Mortality	Adequate allocation concealment, double blinded, 2.4% loss to follow-up, analysis by intention to treat 5
Cantarovich [11]	47 patients with acute kidney injury with urine output < 400 ml.day^{-1} and with a clear diagnosis of the acute kidney injury and no response to mannitol 60 g within 24 h	Control group (n = 13): conventional treatment (details not defined) Furosemide group 1 (n = 19): *fixed* dose of furosemide 600 mg.day^{-1} until diuresis > 2000 ml.day^{-1} Furosemide group 2 (n = 15): *progressive* dose, geometric progression of furosemide from 100 mg (over 30 min) to 3200 mg.day^{-1} (over 10 h). There were no details on the geometric progression criteria	Mortality	Allocation concealment not clear, no blinding, loss to follow-up not reported, analysis by intention to treat not sure 1
Brown [9]	56 patients with acute kidney injury not due to obstruction or dehydration but patients were not necessarily oligo-anuric	Control group (n = 28): iv furosemide 4 mg.min^{-1} for 4 h (total 1 g) Furosemide group (n = 28): iv 4 mg.min^{-1} for 4 h (total 1 g) followed by 2 mg.min^{-1} infusion or oral furosemide 1 g tds to maintain urine output 150–200 ml.h^{-1} till serum creatinine < 300 μmol.l^{-1} without dialysis	Mortality and proportion of patients requiring dialysis	Allocation concealment not adequate, no blinding, loss to follow-up not reported, analysis not by intention to treat not sure 1
Karayannopoulos [12]	20 patients acute renal failure or acute on chronic kidney injury. Patients' details were not described but the age and diagnoses were matched	Control group (n = 10): conventional treatment without furosemide (details not described) Furosemide group (n = 10): 1 g initially and increased to 3 g over a period of 7 days if no response	Proportion of patients requiring dialysis	Allocation concealment not clear, no blinding, loss to follow-up not reported, analysis by intention to treat not sure 1
van der Voort PH [14]	71 mechanically ventilated patients were included when the continuous veno-veno haemofiltration was ceased. The criteria to restart dialysis were occurrence of one of the following: serum urea > 40 mmol.l^{-1}, fluid overload with hypoxia, serum potassium level > 6.0 mmol.l^{-1}, metabolic acidosis, or uraemic syndrome	Control group (n = 35): iv placebo infusion (exact nature not defined) Furosemide group (n = 36): iv furosemide 0.5 mg.kg^{-1}.h^{-1} by continuous infusion. The study medication was stopped when the creatinine clearance appeared to be > 30 ml.min^{-1}. In all other situations, the study medication was continued until the study end point (recovery of renal function) was reached or until a new haemofiltration session was started	Mortality and proportion of patients requiring dialysis	Allocation concealment not clear, Double-blinded, all completed the study, analysis by intention to treat 3
Mahesh B [15]	50 cardiac surgical patients at risk of developing acute kidney injury with ≥ 1 of the following criteria: serum creatinine> 130 μmol.l^{-1}, ejection fraction< 50%, diabetes mellitus, combined coronary artery bypass graft and valve surgery, redo cardiac surgery	Control group (n = 21): 0.9% saline 2 ml.h^{-1} started after induction of anaesthesia and continued until 12 h after surgery. Furosemide group (n = 21): 4 mg.h^{-1} of furosemide at 2 ml.h^{-1} started after induction of anaesthesia and continued for 12 h after surgery	Mortality and proportion of patients requiring dialysis	Allocation concealment not clear, double- blinded, 20% did not complete the study, analysis not by intention to treat 4

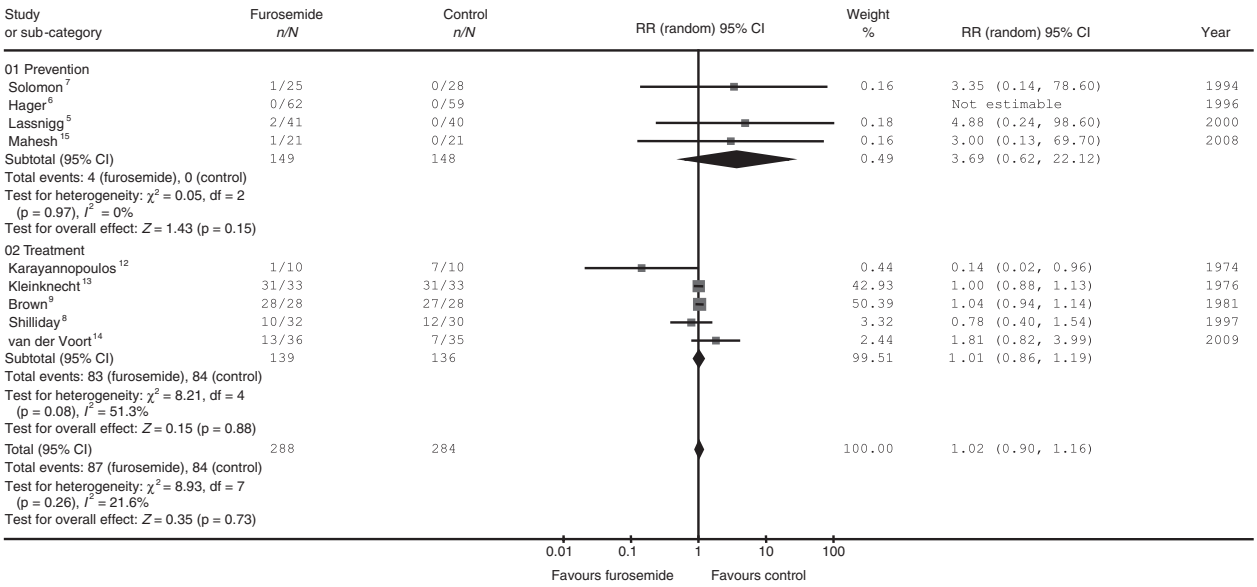

Figure 2 Forest plot showing the effect of furosemide on risk of requiring renal replacement therapy.

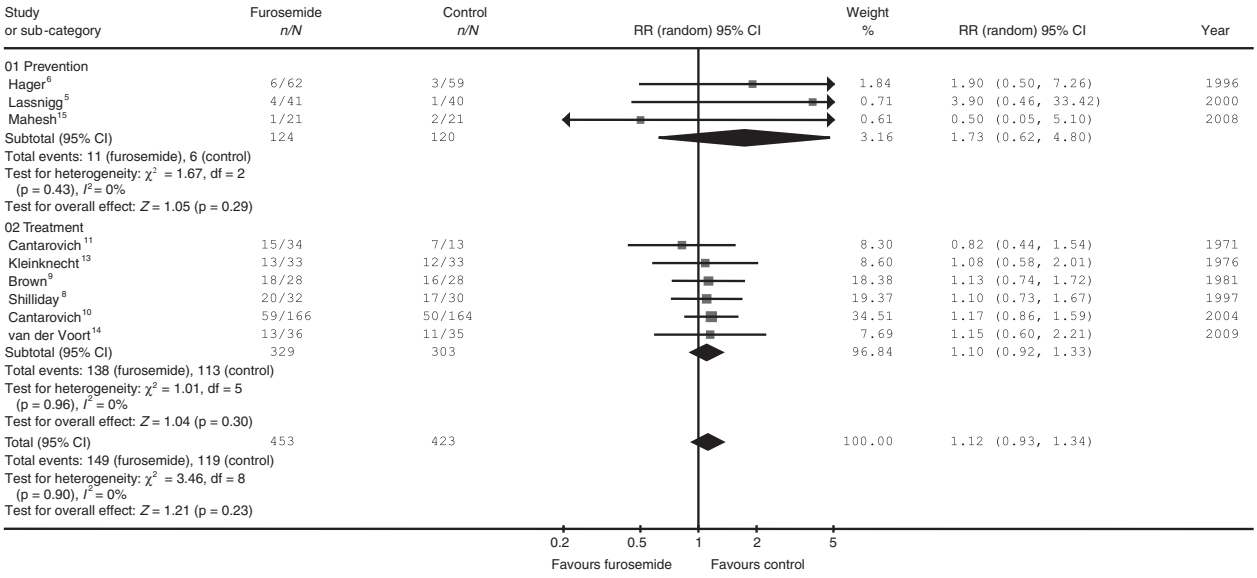

Figure 3 Forest plot showing the effect of furosemide on all-cause mortality.

Although furosemide may not be useful in reducing the risk of renal replacement therapy and mortality *directly*, it may still have a potential role in some clinical situations. First, AKI is commonly associated with cardiovascular failure and acute lung injury as part of a multi-system disease. The mortality of these patients is extremely high [43, 45]. The use of furosemide, as part of a conservative fluid management protocol, may reduce fluid retention and the duration of mechanical ventilation without causing renal failure [47, 48]. It is also worthwhile to note that the risk of developing AKI was reduced when a lung-protective ventilation strategy was used in the ARDS Network trial [49]. Because poor gaseous exchange is one of the possible barriers to implement lung-protective ventilation strategy [50] and a fluid overloaded state may contribute to deteriorations in gaseous exchange, perhaps furosemide may have a role in avoiding fluid retention to facilitate lung-protective ventilation strategies. By adhering to lung-protective ventilation strategies in patients with acute lung injury

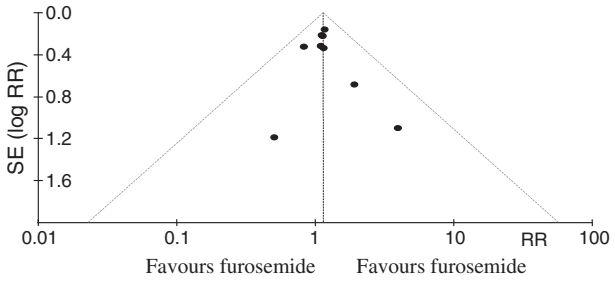

Figure 4 Using all-cause mortality as an end-point, the funnel plot does not suggest publication bias.

without haemodynamic instability [49], furosemide may be useful in preventing AKI *indirectly*.

Second, as expected from the pharmacology of furosemide, the diuretic effect of furosemide depends on renal blood flow, and the function of the proximal tubule and loop of Henle. Clinical observation suggests that non-oliguric AKI is a milder form of AKI than oliguric AKI [3, 4], and a brisk and sustained urinary output response to furosemide at the early stage of AKI may be considered as a 'proxy' for having a mild AKI and has a lower of risk of requiring dialysis [8, 31, 51]. It is, however, the severity of AKI that dictates whether a patient will respond to furosemide; it is not furosemide that determines the severity of AKI.

Third, furosemide can increase the urinary excretion of water, sodium, potassium, acids, and calcium in patients who are still responsive to furosemide. As such, furosemide can be useful for reducing the severity of hyperkalaemia, acidosis, and fluid overload in mild AKI. In patients with hyperkalaemic renal tubular acidosis (Type IV RTA) and hypercalcaemia, furosemide can be considered as a useful adjunct to other medical therapies (Table 3) [16, 52, 53]. Similarly, furosemide may be useful for correcting hyperchloraemic acidosis after a large amount of intravenous 0.9% saline, if the patient is judged to be adequately or excessively hydrated.

Finally, furosemide has been shown to offer some benefits in selected groups of patients who are at risk of AKI. For example, furosemide has been shown to reduce portal hypertension and improve glomerular filtration rate in patients with portal hypertension and ascites, probably through suppression of an activated renin-angiotensin-aldosterone axis [54, 55]. Furosemide also appears to be more effective than mannitol when combined with hydration using 0.9% saline to prevent cisplatin-induced nephrotoxicity [56]. Although furosemide is often used with hydration to enhance uric acid excretion in preventing tumour lysis syndrome, there are no strong observational or randomised controlled trial data to support its effectiveness in this situation. Indeed, recent evidence suggests that a crystal-independent mechanism plays a significant role in AKI related to tumour lysis syndrome [57]. Whether furosemide can offer further benefits in addition to recombinant urate oxidase and other supportive therapies in preventing AKI from tumour lysis syndrome remains uncertain, but this merits further investigation.

Potential pitfalls of using furosemide

First, it is important to emphasise that furosemide can increase urine output without improving the creatinine clearance and renal function. A transient increase in urine output after furosemide may create a false sense of security, as if the drug has 'fixed the problem' or changed the course of AKI. This has the potential to delay the diagnostic and therapeutic process targeting the underlying causes of AKI, such as hypovolaemia, urinary outflow tract obstruction and sepsis. As such, the administration of furosemide should only be considered after close attention to the underlying causes of oliguria and the haemodynamic status of the patient. Adequate hydration is important in determining the diuretic and renovascular protective response to furosemide [30, 37]. Furthermore, a low urinary sodium concentration has been suggested as a means of differentiating between hypovolaemia and normovolaemia in patients with oliguria [58]. Urinary sodium analysis will certainly become useless once furosemide is administered. In healthy individuals, urinary sodium concentrations after intravenous furosemide are between 60 and 70 $mmol.l^{-1}$ resembling 0.45% saline [59]. Similarly, other urinary markers of AKI (e.g. retinol

Table 3 Potential roles of furosemide in patients who are at risk of, or with established, acute kidney injury (AKI).

As a part of the strategy to avoid fluid retention in patients with co-existing acute lung injury so that the ARDS Network lung-protective ventilation strategy can be implemented to reduce the risk of AKI, duration of mechanical ventilation, and length of intensive care unit stay
Using urinary response to furosemide as a prognostic test to predict the risk of requiring renal replacement therapy
Concurrent use of furosemide with octreotide improves glomerular filtration rate, urine output and portal hypertension in patients with portal hypertension and ascites when compared to octreotide alone
As part of the therapy with hydration and bisphosphonates for hypercalcaemia
Furosemide with 0.9% saline is better than 0.9% saline with mannitol in preventing cisplatin-induced nephrotoxicity
To control hyperkalaemia and acidosis in hyperkalaemic renal tubular acidosis which is common in early stages of diabetic nephropathy and interstitial nephritis

binding protein) can also be affected by furosemide, and their urinary concentrations should be interpreted as a ratio to urinary creatinine concentrations [15].

Second, it is tempting to administer repeated large doses of furosemide (e.g. > 1000 mg) to improve the urine output of patients with severe AKI. These patients have the highest risk of ototoxicity from furosemide because the clearance of furosemide is significantly reduced in severe renal failure [17, 18, 60]. The risk of ototoxicity is particularly high when the plasma furosemide concentrations exceed 50 $\mu g.ml^{-1}$ [61], with concurrent aminoglycoside and vancomycin antibiotics [62], and possibly in sedated patients who cannot report symptoms of ototoxicity. Recent evidence suggests that the use of large doses or prolonged furosemide infusion to delay dialysis may in fact be associated with a higher mortality in severe AKI than early dialysis [63, 64].

Third, furosemide can induce aciduria. Acidic urine has been shown to increase the precipitation of urinary glycoprotein (uromodulin, also called Tamm–Horsfall protein) with myoglobin and the vasoconstriction induced by met-myoglobin [65, 66]. Similarly, aciduria may be potentially harmful by inducing nephrotoxic methaemoglobin cast formation in patients with severe intravascular haemolysis [67]. Recently, sodium bicarbonate has been shown to be useful in preventing AKI after cardiac surgery [68]. It is possible that haemolysis during cardiopulmonary bypass contributes to AKI after cardiac surgery [69], and as such, furosemide may potentially be harmful for on-pump cardiac surgery by inducing aciduria. It may, therefore, be prudent to monitor the urinary pH and consider concurrent sodium bicarbonate therapy if furosemide is used in patients with rhabdomyolysis or haemolysis. Furthermore, aciduria has also been suggested to promote free radical formation by radiocontrast, and this explains why furosemide may be harmful and sodium bicarbonate or acetazolamide may be protective in preventing contrast nephropathy [7, 70–73].

Finally, furosemide has some unwanted systemic effects. High doses of furosemide can precipitate vasoconstriction and may be harmful in patients with poor myocardial function [74]. Na-K-Cl_2 co-transporters are present in the respiratory tract and furosemide may potentially affect mucociliary function and mucus clearance [75]. Furosemide has some significant drug interactions. Furosemide reduces the clearance of theophylline, other organic acids, and gentamicin [76, 77]. It reduces the therapeutic effect of warfarin [78], but increases the hypokalaemic effect of amphotericin, the anti-epileptic effect of sodium valproate the [79], the hypotensive and renal effect of

Table 4 Potential pitfalls of using furosemide in patients who are at risk of, or with established, acute kidney injury (AKI).

An improvement in urine output can be misinterpreted as an improvement in renal function, delaying the diagnostic and therapeutic process for the underlying causes of AKI.
Induces hypovolaemia, hypokalaemia, hypophosphataemia, hypomagnesaemia, and metabolic alkalosis
Limits the use of urinary sodium concentrations to differentiate between hypovolaemia and normovolaemia
Delaying renal replacement therapy may increase mortality
Induces ototoxicity at high doses in patients with reduced renal clearance of furosemide
High doses can induce systemic vasoconstriction
Reduces mucociliary transport and sputum clearance by inhibiting Na-K-Cl_2 co-transporters of the respiratory tract
Acidifies urine and reduces solubility of myoglobin and haemoglobin in patients with rhabdomyolysis and intravascular haemolysis (including cardiopulmonary bypass), respectively. Aciduria may also promote free radical formation in the urine by radiocontrast agents
Drug interactions: (i) reduces clearance of theophylline, gentamicin, and other organic acids (benzylpenicillin, cephalosporins, oxypurinol, bumetanide, active metabolite of oseltamivir); (ii) increases the risk of amphotericin-induced hypokalaemia, anti-epileptic effect of valproate, hypotensive effect of angiotensin-converting-enzyme inhibitors; (iii) reduces therapeutic effect of warfarin, but warfarin also reduces the diuretic effect of furosemide

Table 5 Special considerations for intra-operative use of furosemide by anaesthetists.

Furosemide has no benefits and is possibly harmful when used with radiocontrast agents, in patients with rhabdomyolysis, and during on-pump cardiac surgery
Furosemide (and dehydration) may aggravate acute kidney injury when used with concurrent nephrotoxic agents such as aminoglycoside, vancomycin, and non-steroidal anti-inflammatory drugs
Furosemide will make urine output no longer a useful end-point for fluid resuscitation and should be avoided, unless an alternative end-point for intravascular volume resuscitation is available (e.g. central venous pressure, central venous oxygen saturation, oesophageal Doppler cardiac output monitor)
A small dose of furosemide (< 10 mg) can be considered to correct hyperchloraemic acidosis induced by a large amount of intravenous 0.9% saline in patients who are not hypovolaemic
If intravenous furosemide is used to replace oral furosemide, only half of the oral dose is required. Intravenous furosemide is about twice as potent and faster than oral furosemide in inducing diuresis

angiotensin-converting-enzyme inhibitors [80], and the risk from ototoxicity from aminoglycosides and vancomycin (Table 4) [60]. The specific considerations for intraoperative use of furosemide by anaesthetists are described in Table 5.

Conclusion

The current evidence from randomised controlled trials and observational studies suggests that furosemide is unlikely to be able to improve renal function or mortality *directly*. In patients with acute lung injury without haemodynamic instability, furosemide may be useful in avoiding fluid retention to facilitate mechanical ventilation. The pharmacology of furosemide and observational data suggest that patients with mild AKI will respond to furosemide better than patients with severe AKI. If furosemide is used carefully, it may still have a clinical role in some patients with mild AKI.

Competing interests

None declared.

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