CRITICAL CARE

Systematic review: The use of diuretics and dopamine in acute renal failure: a systematic review of the evidence

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Abstract

Objective: To evaluate the impact of diuretics and dopamine for both the prevention and treatment of renal dysfunction in the acute care setting.

Study identification and selection: Studies were identified via MEDLINE, and through bibliographies of primary and review articles. Articles were then screened by the author for studies addressing the use of diuretics or dopamine in the prevention and/or treatment of renal dysfunction.

Data abstraction and literature appraisal: From individual studies, data were abstracted regarding design features, population, intervention and outcomes. Studies were graded by levels according to their design.

Results: A total of 10 studies using diuretics and 30 involving dopamine were identified. Level I evidence exists against the use of diuretics for radiocontrast-induced acute tubular necrosis, and loop diuretics given after vascular surgery. There is level II evidence that diuretics do not improve outcome in patients with established acute renal failure. Level II evidence also exists against the use of dopamine in the prevention of acute tubular necrosis in multiple subsets of patients.

Conclusions: Routine use of diuretics or dopamine for the prevention of acute renal failure cannot be justified on the basis of available evidence.

Introduction

The term acute renal failure (ARF) has been used to encompass a wide variety of clinical disorders ranging from glomerulonephritis to prerenal azotemia. It is generally defined as a rapid decline (within hours to weeks) in glomerular filtration rate (GFR) and retention of nitrogenous waste products. Each underlying disorder has its own unique pathophysiology and separate set of etiologies. Furthermore, many of these clinical syndromes have specific treatments. Accordingly, it is not possible to consider the issue of whether diuretics or dopamine are useful in ARF without first considering the differences between these individual disorders. Moreover, data drawn from animal experiments, where compounds such as uranyl nitrate or glycerol were used to induce ARF, must be interpreted with caution [1]. Still, much of our understanding of these disorders, and

the effects of various treatments, comes from these models. In general, diuretics and/or dopamine are usually considered for the prevention or treatment of acute tubular necrosis (ATN). The basic rationale is that ischemic ATN should be improved by increasing renal blood flow and that tubular obstruction should be decreased by maintaining urine flow.

The use of diuretics to prevent or even 'treat' renal dysfunction has become a widely accepted clinical practice. Indeed, management protocols for some routine patients often include orders for furosemide when urine output falls below some cutoff value. Some protocols even utilize socalled 'renal-dose' dopamine in these circumstances. It is therefore necessary to review the evidence in support of such practices. Given the broad range of conditions predisposing to ARF and the multiple comorbidities of critically ill patients, a systematic review addressing the effect of different treatments must be interpreted in light of these clinical features.

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Therefore, the purpose of this review was to evaluate the impact of diuretics and dopamine for both the prevention and treatment of renal dysfunction in the acute care setting.

Methods

Search strategy

A MEDLINE search was conducted using databases from 1966 to May 1997. Articles dealing with kidney (drug effects) and diuretics or dopamine were searched. This pool of articles was then limited to English language clinical trials or meta-analyses of human studies. Bibliographies of review articles on these topics were also searched by hand for additional studies meeting the above criteria. This group of articles was then screened by the author for studies addressing the use of diuretics or dopamine in the prevention and/or treatment of ARF.

Inclusion and exclusion criteria

For the purpose of this review only loop diuretics, mannitol and dopamine were included. Loop diuretics included the agents furosemide, bumetanide and torsemide. These agents have become the most widely used for the indications considered in this review. Although ethacrynic acid is also a loop diuretic, it was excluded because it is not commonly used in clinical practice. Additionally, other diuretic agents such as thiazides were excluded. Similarly, this review will not discuss any of the yet experimental agents such as atrial natriuretic factor. The primary analysis included only studies that involved humans and were published in English.

Critical appraisal methods

Individual studies were graded by levels according to the criteria in Table 1, adapted from Cook *et al* [2]. When multiple studies were available, the highest level study

Table 1 Levels of evidence for treatment effect

Level I	Randomized trials with low false positive (α) and low false negative (β) error (ie high power)
Level II	Randomized trials with high α error or low power
Level III	Non-randomized concurrent cohort studies
Level IV	Non-randomized historic cohort studies
Level V	Case series

Adapted from Cook *et al* [2].

was used. Clinical trials of the effectiveness of diuretics or dopamine were judged to be effective only if the outcome measures were of clinical significance (eg mortality, need for hemodialysis) or in terms of biochemical evidence of organ function (serum creatinine or creatinine clearance) following the maneuver. Surrogate markers such as urine output or renal blood flow were not considered as evidence of effectiveness. Furthermore, trials of dopamine were not considered controlled unless confounding variables such as blood pressure and cardiac output were reported. Similarly, for both diuretics and dopamine, the volume status of the control and treatment groups must have been similar.

Results

The literature search results are shown in Table 2. Seven diuretics studies were located via MEDLINE and another three from review article bibliographies [3-12]. For dopamine these numbers were 13 and 17, respectively [13-42]. The results of the critical appraisal are shown in Tables 3–4. Studies evaluating the effectiveness of these agents in ATN were divided into three clinical scenarios:

1. prevention of radiocontrast-induced ATN;
2. prevention of ischemic ATN, and
3. treatment of established ATN.

Radiocontrastinduced ATN

Radiocontrast-induced ATN is rare in patients without underlying renal, cardiac or hepatic dysfunction and occurs most commonly in patients with diabetic nephropathy [43]. In this group the incidence approaches 50%, depending on the degree of baseline renal function and the use of ionic *vs* nonionic contrast media [44]. Several forms of therapy have been proposed to prevent or treat radiocontrast-induced ATN, including saline, furosemide, mannitol, calcium channel blockers, dopamine, atrial natriuretic peptide and theophylline [44]. There are no placebo controlled trials testing the effectiveness of any of these therapies. Virtually all studies have used hydration (usually with 0.45% saline) in addition to the agent being tested and most authors recommend its use. However, even then, little comparative data exist for these potential treatments. One exception is the study

Table 2 Literature search results

	Diuretics	Dopamine
Total number of trials	10	30
Number fulfilling outcomes criteria	8	20
Radiocontrast ATN	2	2
Prevention of ischemic ATN	5	16
Treatment of ATN	3	12

ATN = acute tubular necrosis.

Table 3 Evidence for loop diuretic therapy in acute tubular necrosis (ATN)

Indication (result)	Strength of evidence	Source
Radiocontrast ATN		
For prevention (no)	Level I	Solomon *et al* [3]
Ischemic ATN		
For prevention (?)	No data in humans	
Vascular surgery (no)	Level I[*]	Hager *et al* [8]
Treatment of ATN		
Rhabdomyolysis (no)	Level IV	Better *et al* [7]
Improves outcome (no)	Level II	Kleinknecht *et al* [11]

[*]Loop diuretics were begun after surgery and continued through the ICU stay.

by Solomon *et al* [3] which compared the effects of furosemide plus saline, mannitol plus saline and saline alone; again, 0.45% saline was used. This randomized trial of 78 'high-risk' patients found that both diuretic regimens were less effective in preventing ATN than saline alone (relative risk of ATN using mannitol 2.5 or furosemide 3.6 *vs* saline alone; $P = 0.02$). Another study, by Weinstein *et al*, found that renal function

Table 4 Evidence for low-dose dopamine therapy in acute tubular necrosis (ATN)

Indication (result)	Strength of evidence	Source
Prevention of ATN		
Critically ill/sepsis (no)	Level II	Lherm *et al* [14]
Cardiothoracic/ vascular surgery (no)	Level II	Myles *et al* [23]
Liver transplantation (no)	Level II	Swygert *et al* [30]
Renal transplantation (no)	Level II	Grundman *et al* [39]
Treatment of ATN		
Critically ill/sepsis (?)	No data available in humans	
Surgery (no)	Level V	Flancbaum *et al* [13]

significantly deteriorated in patients pretreated with furosemide [4].

As shown in Table 1, to date only two clinical trials have been published using dopamine to prevent radio-contrastinduced ATN. Hall *et al* [28] studied the effects of dopamine infusion on serum creatinine assessed at day 3 after radiocontrast administration in patients with baseline serum creatinine levels of > 2.0 mg/dl. This level III study did show an improvement in serum creatinine with dopamine compared to a control group which received mannitol. However, given the evidence that mannitol may actually be harmful in this setting [3], this was probably not the appropriate control group. In the only other controlled trial, Weisberg *et al* [24] found no difference in the incidence of ATN with or without dopamine (30–40%) in a small series of patients ($n = 30$). Thus, for this indication we can safely conclude that diuretics and dopamine are clearly not helpful and may even be harmful, while volume expansion with 0.45% saline is unproven but potentially beneficial.

Prevention of ischemic ATN

Of the five studies listed in Table 1, only one trial used loop diuretics. Hager *et al* [8] randomized 121 patients to receive either furosemide (1 mg/h) or placebo starting immediately after major thoraco-abdominal or vascular surgery and continuing throughout the intensive care unit (ICU) stay. The authors measured creatinine clearance and found no difference between furosemide and placebo. Unfortunately, the study was unable to address the use of loop diuretics given during the procedure.

The facts are even less clear regarding mannitol in vascular surgery. The only controlled study available is by Beall *et al* from 1963 [5]. This study compared the outcomes of 30 patients who underwent elective abdominal aortic aneurysm repair. Patients were randomized to receive either no pre-operative fluid, iv hydration only or iv hydration plus mannitol as required to keep urine output > 60 ml/min. There was no change in renal function or postoperative urine output between the latter two groups. Although this negative study was certainly underpowered, it remains the only controlled trial of mannitol in vascular surgery to date. The following year, Powers *et al* reported the outcomes of 104 patients treated with mannitol [6]. This uncontrolled study reported that all patients had an increase in urine output and none developed ATN. No recent studies have been carried out to address this issue and it is unlikely that any will. In other types of surgery, such as coronary artery bypass [9] or biliary surgery [10], small studies have also been unable to demonstrate a benefit associated with mannitol. Given these considerations, and in the absence of clinical data, diuretics cannot be recommended to prevent ATN.

Thirty clinical studies of dopamine have been published to date, both for prevention of ATN and treatment of early ATN (including radiocontrast-induced ATN). However, only 20 of these used outcomes other than surrogate markers (eg urine output, renal blood flow), and only three were positive. These included the study by Hall *et al* [28], cited above, and two others which were both methodologically inferior, one level IV and one level V. Polson *et al* [38] found a significant difference in creatinine clearance and a decrease in ARF in liver transplant patients treated with 2 µg/kg/min dopamine. The findings of this level IV study were not supported by a level II study from Swygert *et al* [30], also in liver transplant patients. The Swygert study used 3 µg/kg/min dopamine and found no difference compared to placebo in terms of creatinine clearance or incidence of ARF (4% in both groups). The results of a small level V study by Palmieri *et al* [26] appear to suggest that dopamine may be useful in shortening the recovery time from interleukin-2-induced ARF. Apart from these two studies, the remaining 17 [13-25,27,29-37,39-42], collectively enrolling over 700 patients, are all negative. Among these is a recent level II study by Lherm *et al* [14] in which dopamine infusion failed to improve renal function in patients with sepsis except for transiently increasing creatinine clearance in patients without shock.

Treatment of established ATN

Of the three trials evaluating the use of diuretics in the treatment of ATN, two fulfilled outcome criteria. Both studies evaluated the effects of treatment on mortality and the need for dialysis. In the first, Kleinknecht *et al* [11] randomized 66 patients to receive furosemide or placebo. Although, the furosemide group did experience improved urine output, there were no significant differences between the two groups in terms of renal recovery, days on dialysis or mortality. A second study by Brown *et al* [12] had similar results. In this study, 58 patients were given a single dose of furosemide (1 g) and then randomized either to receive or not receive continued diuretic therapy; again, there were no differences between the two groups in terms of need for dialysis or survival. Unfortunately, even the two studies together lack sufficient power to entirely rule out the possibility that diuretics have a beneficial effect on survival. Nonetheless, the available literature to date does not support a survival benefit for this therapy.

Discussion

The idea that the emperor indeed 'has no clothes' may be difficult for some clinicians to accept. The use of diuretics and low-dose dopamine to prevent or treat renal dysfunction in the operating room or ICU has become routine in many centers. One might ask how this all came to be in the first place; are there not sound theoretical grounds on which to build a case for these interventions? Is it not likely that all or most of these studies are sufficiently under-powered to have missed a clinically significant effect? Indeed, Tables 3 and 4 contain very few level I studies. However, on closer scrutiny the theoretical grounds which form the basis for these therapies are beginning to give way under the weight of some new experimental evidence.

Diuretics and ATN

Experimentally, the effectiveness of diuretics in the prevention of ischemic ATN appears to be related to timing. While no data exist in humans, several lines of evidence from animal experiments suggest that interventions such as diuretics may be useful if given within minutes (or perhaps the first few hours) following a renal insult [1]. Once this time limit has passed, the intervention will be ineffective. This is because the unifying principle is cytoprotection of the renal tubular cells which, if lethally injured, may only be 'rescued' for a short time. The injury to the renal tubular cells has been attributed to four major factors: renal vasoconstriction, reduction of glomerular capillary permeability, tubular obstruction and transepithelial back-leak of filtrate [45]. In theory, loop diuretics may be useful in combating each of these factors. These agents decrease the metabolic demand of the renal tubular cell, reducing its oxygen requirement and hence increasing its resistance to ischemia [46] and perhaps to other toxic insults as well. A greater urine flow may also reduce the incidence of tubular obstruction and the higher hydraulic pressures may reduce the back-leak of filtrate [47]. In the latter case, fluid resuscitation alone may produce much of the same effect [7].

In practical terms these data from animal studies offer little to guide practice in the care of patients, though they provide great insight into the various mechanisms of ATN. This is because it is not usually possible to anticipate the renal injury and act within the time required to have an effect. However, there are notable exceptions, such as aortic cross-clamping in aneurysm repair. The use of loop diuretics has become routine for this indication in many institutions. Nonetheless there appears to be no evidence in support of this approach.

Additionally, there are some situations in which the renal injury is subacute or mild and sustained. Such is often the case in conditions such as rhabdomyolysis, drug-induced renal injury, hepatorenal syndrome, and ARF associated with cardiopulmonary bypass circulation in cardiac surgery (especially in patients with pre-operative renal impairment [48]). In these conditions it is often possible to act in an attempt to prevent or reduce

the renal injury as it evolves. Although the specifics of renal injury vary somewhat between these forms of 'sub-acute' renal failure, all are exacerbated by hypovolemia and, therefore, any consideration of the use of loop diuretics must include a provision for adequate volume replacement. This requirement makes it difficult to separate the effects of diuretics from the effects of the increased fluid given to prevent diuretic-induced hypovolemia. Dramatic evidence exists from a case-controlled study to support the use of ('early and aggressive') hydration along with forced alkaline/osmotic diuresis (mannitol) for the treatment of ATN secondary to traumatic rhabdomyolysis [7]. In this study, delayed treatment in a series of seven patients was associated with a 100% incidence of ARF, while in another seven patients prompt treatment was 100% successful in avoiding this complication even though renal injury had already begun. Unlike loop diuretics, mannitol functions as an intravascular volume expander, at least initially, and may also function as a free-radical scavenger. None of these patients received loop diuretics and, indeed, the authors have argued that hydration alone may have been sufficient to produce many of salutary effects of the osmotic diuresis [7].

Once ATN is established there are no therapies that have been proven to reverse it. The most a clinician can do is to manage the complications of ARF and limit further renal insult so as to assure the best chance of renal recovery. Diuretics can be both useful and harmful in this regard. The harm comes from reducing the circulating volume too much and adding a prerenal insult on top of the established ATN. The recovering kidney may be even more susceptible to this 'second hit' and may be profoundly injured by a relatively mild decrease in perfusion, especially with the pre-existing renal disease. Clinicians may inadvertently produce this injury if diuretics are dosed according to the amount of peripheral edema or body weight without consideration of intravascular volume. This may be of particular concern in many critically ill patients with hypoalbuminemia. These patients may have coexisting total body volume overload and intravascular volume depletion.

However, if volume status is monitored closely, diuretics can be useful in the conversion to nonoliguria. This goal may be reasonable in certain situations and patients are clearly easier to manage without volume overload and electrolyte imbalances. In this regard, loop diuretics appear to be more effective and less toxic when given as a continuous infusion rather than as a bolus. In a randomized, crossover trial, Rudy *et al* [49] evaluated the effectiveness of continuous infusion *vs* bolus dosing of bumetanide. Continuous infusion produced 48 mmol more net sodium excretion (95% CI 16–80 mmol, *P* = 0.01), and less toxicity. It is also important to note that large bolus doses of loop diuretics may cause transient renal vasoconstriction. Despite these potentially useful effects of diuretic therapy, there is no evidence that converting oliguria into nonoliguria is effective in reducing mortality or the need for dialysis. As detailed above, this question has now been evaluated in two randomized trials [11,12].

Medullary ischemia, renal blood flow and dopamine

In general, ATN occurs more commonly in patients with certain types of underlying physiologic states or diseases (elderly, relative hypovolemia, diabetes, underlying kidney disease, heart disease, hepatic cirrhosis, certain autoimmune diseases and malignancies) as well as in certain clinical settings (sepsis, surgery, trauma, drug-induced). Indeed, one of the most commonly anticipated etiologies of ATN is the use of iv contrast agents for imaging studies [43]. Although the pathogenesis of renal injury secondary to radiocontrast agents is not entirely understood, it appears to be due to medullary ischemia [3,50]. For some time, it has been postulated that this ischemic injury occurs on the basis of decreased renal blood flow secondary to renal vasoconstriction. It is therefore surprising that studies have now shown that renal blood flow actually increases with radiocontrast [24]. This has led some investigators to hypothesize that medullary ischemia is a demand-side phenomenon. In other words, the ionic load leads to medullary ischemia because the medullary cellular oxygen demand becomes greater than the supply [51,52]. This aspect of renal physiology also has implications for the use of agents like dopamine.

Like loop diuretics, dopamine is frequently used by clinicians to increase urine output in ARF in the hope that such a maneuver might attenuate renal injury or improve survival. Much of the enthusiasm for this agent comes from the belief that dopamine increases renal blood flow and that such an outcome is in fact desirable. Additionally, clinicians often interpret an increase in urine output as proof that these two assumptions are valid. Indeed, dopamine may increase urine output through four separate mechanisms. Dopamine stimulates both dopaminergic and adrenergic (both alpha and beta) receptors. As such, dopamine may affect renal blood flow by direct vasodilatation (dopamine receptors), by increasing cardiac output (beta receptors) or by increasing perfusion pressure (alpha receptors). At lower doses, particularly less than 2 μg/kg/min, the dopaminergic effects tend to predominate, although wide variability appears to exist across patients and clinical conditions. In the appropriate clinical setting, any of these mechanisms might increase effective renal plasma flow and thus increase urine output. Under such conditions, the increase in urine output might well be

indicative of improved renal function. However, dopamine may increase urine output by yet a fourth mechanism, that of inhibition of sodium-potassium ATPase at the tubular epithelial cell level [53]. The effect of this final mechanism is to increase sodium excretion and thereby diuresis. Thus, apart from its direct and indirect effects on the renal vasculature, dopamine increases urine output because it is a diuretic.

The natriuretic/diuretic effects of dopamine are of importance not only because they may lull clinicians into believing that they are improving renal function when they observe an increase in urine output with the drug, but also because this increase in urine output may come with unexpected effects. Most 'enthusiasts' use so-called 'renal-dose dopamine' in the belief that they can improve renal blood flow and that this will restore oxygen delivery to portions of the kidney that are dysoxic. Unfortunately, as already discussed, the problem may not be remedied simply by increasing total renal blood flow. This is because the area of the kidney that is most at risk from ischemia is the very area least likely to benefit from dopamine infusion. This area is the outer medulla. Normally, outer medullary cells live on the edge of dysoxia. Oxygen diffuses from the descending to ascending vasa recta within the vascular bundles limiting oxygen delivery to the renal medulla [52]. In addition the medulla suffers from unusually high oxygen demand related to tubular transport activity (medullary oxygen extraction approaches 90% [54]. Thus, the renal medulla is constantly on the brink of dysoxia owing to high demand and low delivery of oxygen.

Given these considerations, it is certainly understandable for clinicians to desire to increase renal blood flow in the hope of improving medullary oxygen delivery. However, Heyman *et al* have recently demonstrated that although dopamine increased outer medullary blood flow in the hypovolemic rat, it failed to improve outer medullary dysoxia [55]. In fact, analogous to the situation with radio-contrast, the increase in solute delivery to the distal tubular cells produced by the natriuretic effects of dopamine (via inhibition of proximal tubular reabsorption) might actually increase their oxygen consumption and therefore increase rather than decrease the risk of ischemia [56].

With these 'myths' of experimental evidence dispelled, or at least severely questioned, it is not surprising that clinical trials have failed to demonstrate a beneficial effect from dopamine infusion in the setting of treatment or prevention of ATN [57,58]. Data of this sort also call into question the appropriateness of increasing urine output in the first place. As we have seen with other types of diuretics, converting oliguric to nonoliguric renal failure may provide certain management advantages, but does not affect overall renal recovery or outcome. Accordingly, on the basis of existing evidence, the use of dopamine to improve renal function cannot be recommended. This is not to say that dopamine is not a useful drug. Indeed, dopamine's multiple effects (even at low doses) make it the perfect pressor/inotropic agent when such a combination is warranted. It is a common clinical scenario in which a patient is both modestly hypotensive/vasodilated and has a degree of cardiac dysfunction. Such a patient may well benefit from the combined inotropic, vasopressor, renal vasodilator and diuretic effects of this drug. However, as always, when safer or less invasive alternatives are available, they should be used first. For example, loop diuretics are much more effective diuretics than dopamine and are much safer. Similarly, dobutamine would be a better alternative for the patient who primarily requires an inotrope, and norepinephrine would be a better choice for a vasodilated, hyperdynamic patient.

Certainly, dopamine has a number of potential disadvantages. In a recent study, Segal *et al* demonstrated that low-dose dopamine caused earlier onset of gut ischemia [59]. Even at low doses, dopamine may increase cardiac contractility and systemic resistance, and can cause tissue necrosis and digital gangrene [60]. Furthermore, even if dopamine were without risk, its effects can be unpredictable. This point was stressed by Flancbaum *et al*, who demonstrated that low-dose infusion alone produces a drug-dependent increase in the urinary output in oliguric, euvolemic ICU patients, and that the maximal effect is temporally variable [13]. Given the fact that the renal effects of low-dose dopamine in patients with sepsis syndrome decrease with time, it has been suggested that there is a desensitization of renal dopaminergic receptors [14]. The above considerations argue against the routine use of 'renal-dose dopamine' for patients with renal insufficiency.

Conclusions
The use of diuretics in the management of ARF remains controversial despite several advances in the understanding of the pathogenesis of renal failure and the mechanisms of action of the agents commonly used to manage it.

At the present time the limited observational and experimental evidence available moderately supports the following guidelines:

1. For prophylaxsis against radiocontrast-induced ATN, saline infusion should be administered for optimal hydration; neither diuretics nor dopamine appear effective and may be harmful.

2. For the prevention of ischemic ATN, although animal data suggest this intervention would be helpful, there are no human data to support the use of diuretics.

3. The use of 'renal-dose dopamine' has not been substantiated to improve outcome in human studies and may prove to be deleterious in certain clinical settings.

4. In the management of rhabdomyolysis, loop diuretics should probably be avoided, although mannitol may be effective on the basis of level IV evidence.

5. When loop diuretics are used in the management of ARF, continuous infusion may be more efficacious than bolus administration in achieving diuresis. However, there is no evidence that this maneuver improves survival or renal recovery.

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