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Prevention of Acute Renal Failure

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Abstract

Acute renal failure is one of the most common organ failures occurring in critically ill patients. Mortality rates remain high despite treatment. This article will discuss the goals of prevention, pharmacologic and non-pharmacologic strategies including the role of diuretics and vasoactive agents, and will briefly consider future directions.

Keywords: Acute renal failure, diuretics, dopamine, acetylcysteine, acute tubular necrosis, contrast nephropathy

Introduction

Acute renal failure (ARF) is said to affect from 5 to 20% of all ICU patients and is associated with a mortality rate of 28 to 90%. In many ways, its nature and epidemiology resemble those of other loosely defined ICU syndromes, such as severe sepsis, septic shock or ARDS. Clearly efforts to understand the pathophysiology, to prevent or to treat, and even to better define ARF are urgently needed.

Goals of Prevention

The goals of a preventive strategy for the syndrome of ARF are to preserve renal function, to prevent death, to prevent complications of ARF (volume overload, acid-base disturbances, and electrolyte abnormalities); and to prevent the need for chronic dialysis, with minimum adverse effects. Surrogate outcomes should be limited to measurements of biochemical evidence of organ function (serum creatinine or creatinine clearance) after the intervention. Surrogate markers such as urine output or renal blood flow should not be considered as evidence of effectiveness.

Non-Pharmacologic Strategies to Prevent ARF

Conservative methods to prevent ARF by limiting dehydration, hypotension and exposure to nephrotoxins are the mainstay of prophylaxis. Four particular strategies are worth reviewing—fluids, aminoglycoside dosing, lipid preparations of amphotericin, and non-ionic contrast agents. While there are no RCTs comparing fluids with no intervention. RCTs have combined fluids (especially 0.45% sodium chloride infusion) with other active treatments. Comparisons between outcomes in these trials and historical untreated controls are difficult but suggest benefit from fluids [1]. In certain settings, such as traumatic rhabdomyolysis, early and aggressive fluid resuscitation has had dramatic benefits compared with historical controls [2]. One RCT (n =1620) compared hydration using 0.9% saline infusion with 0.45% saline in dextrose for prevention of radiocontrast induced nephropathy, in patients undergoing coronary angiography [3]. This study found that hydration with 0.9% saline infusion significantly reduced radiocontrast induced nephropathy (0.7% with 0.9% saline *v* 2% with 0.45% saline; P = 0.04).

Aminoglycosides, amphotericin and radiocontrast are the most commonly encountered nephrotoxins in the ICU. One RCT (n = 85) compared once daily with three times daily dosing of gentamicin [4] and found equal efficacy but significantly less incidence of nephrotoxicity with single dosing (2/40 [5%] with single dosing *v* 11/45 [24%]; RR 0.21, 95% CI 0.05 to 0.87; NNT 5, 95% CI 2 to 24). The use of lipid formulations of amphotericin B seems to cause less nephrotoxicity compared with standard formulations, but direct comparisons of long-term safety are lacking. Currently there is no definitive evidence (sufficiently powered RCTs) that lipid formulations of amphotericin B result in less ARF. However, data from a phase II trial of a

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lipid formulation of amphotericin B (n = 556) found an incidence of renal toxicity (defined by any increase in serum creatinine) of 24%. This compares with 60-80% incidence reported with standard formulation of amphotericin B. In addition, patients with baseline serum creatinine in excess of 2.5 mg/dL on standard amphotericin B showed a significant decrease in serum creatinine when transferred to the lipid formulation (P< 0.001) [5]. One systematic review (31 RCTs, 5146 patients) comparing low osmolality contrast media with standard contrast media [6] found low osmolality contrast media did not influence the development of ARF or need for dialysis (these are rare events), but there was less nephrotoxicity with low osmolality contrast media. The overall benefit was small for people without prior renal failure (OR 0.75, 95% CI 0.52 to 1.10), and was greatest in people with underlying renal impairment (OR 0.50, 95% CI 0.36 to 0.68).

Diuretics

One systematic review comparing fluids alone compared with diuretics in people at risk of ARF from various causes [7] found no evidence of benefit associated with diuretics. Diuretics seem to worsen outcomes in acute tubular necrosis induced by contrast media, and after cardiac surgery. One RCT (n = 78) found that ARF (defined as an increase in serum creatinine >0.5 mg/dL at 48 h) was significantly more likely to occur when people were treated with furosemide plus 0.9% saline (10/25 [40%] *v* 3/28 [11%] with 0.9% saline alone; RR 3.73, 95% CI 1.16 to 12.10; NNH 4, 95% CI 2 to 17) [1]. Another RCT found that furosemide compared with 0.9% sodium chloride was associated with the development of postcardiac surgery acute renal failure (6/41 [15%] with furosemide *v* 0/40 [0%] with sodium chloride; NNH 6, 95% CI 3 to 34) [8]. In the largest study to date, Mehta et al. studied 552 patients to determine whether the use of diuretics alters outcomes in patients with ARF [9]. This study examined patients at the time of nephrology consult so there are limitations to applying its results to the prophylaxis. Still, the authors concluded that after adjustment for relevant covariates and propensity scores, the use of diuretics was associated with a significantly higher risk of death and non-recovery of renal function (Odds ratio 1.77; 95% CI 1.14-2.76). Despite its limitations, this study provides further evidence that diuretics are not helpful and may be harmful in the setting of ARF. The time honored practice of trying to convert oliguric to non-oliguric ARF should be reexamined. Several small RCTs have found no decrease in the incidence of ARF with mannitol over hydration alone in a variety of conditions, including coronary artery bypass surgery [10], traumatic rhabdomyolysis [11], vascular [12], or biliary tract surgery [13].

Dopamine and Dopamine Receptor Agonists

Compared with placebo, dopamine is not effective in the prevention of acute renal failure. Two systematic reviews [14,15] and one subsequent large RCT [16] using dopamine for the prevention of acute renal failure failed to show a benefit. The first meta-analysis [14] was found that dopamine compared with placebo did not prevent mortality (4.7% with dopamine *v* 5.6% with placebo; RR 0.83, 95% CI 0.39 to 1.77), onset of acute renal failure (15.3% with dopamine *v* 19.5% with placebo; RR 0.79, 95% CI 0.54 to 1.13), or need for dialysis (13.9% with dopamine *v* 16.5% with placebo; RR 0.89, 95% CI 0.66 to 1.21). The subsequent RCT, which is the largest to date (328 critically ill people with signs of sepsis), evaluated dopamine in early renal dysfunction. It found that dopamine compared with placebo had no significant effect on the development of acute renal failure (peak serum creatinine concentration during treatment was 2.7 ±1.6 mg/dL in the dopamine group *v* 2.8 ±1.6mg/dL in the placebo group; P = 0.93), the requirement of dialysis (35/161 [22%] with dopamine *v* 40/163 [25%] with placebo; RR 0.89, 95% CI 0.58 to 1.30), intensive care unit length of stay (13 ±14 days with dopamine *v* 14 ±15 days with placebo; P = 0.67), hospital length of stay (29 ±27 days with dopamine *v* 33 ±39 days with placebo; P = 0.29), or mortality (69/161 [43%] with dopamine *v* 66/163 [40%] with placebo; RR 1.06, 95% CI 0.8 to 1.33). A more recent systematic review including many of the same studies reached similar conclusions, namely, no benefit associated with dopamine [15]. Of note, the increase in urine output associated with dopamine is often thought to be caused exclusively by the increase in renal blood flow and, therefore, it may be confused with evidence of benefit. However, dopamine also has a significant diuretic effect.

There is conflicting evidence with regards to the efficacy of fenoldopam in the prevention of ARF secondary to radio-contrast agents. Although several small RCTs [17-20] and one systematic review [21] have shown that fenoldopam increases renal blood flow, renal plasma flow, and creatinine clearance, there is no evidence from RCTs that clinical outcomes are improved. Further, fenoldopam may cause hypotension and therefore can predispose to ARF by reducing renal perfusion pressure [22].

Other Agents

Numerous agents including N-acetylcysteine (NAC), natriuretic peptides, theophylline and calcium channel blockers have been trialed for the prevention of ARF in numerous settings. Only NAC has been shown to be of potential benefit. By pooling the results of several underpowered studies, Brick and colleagues [23] determine that prophylaxis with

oral NAC can indeed result in protection against radio-contrast induced ARF. Their results demonstrated a RR 0.44 (0.22 – 0.88) in favor of treatment. Given the low cost and side effect profile of NAC, it would seem prudent to provide NAC along with intravenous fluids to all patients with these risk factors who are receiving intravenous radio contrast.

Conclusion

ARF complicates the clinical course of as many as 5% of all hospitalized patients. The critically ill and injured are disproportionably at risk and mortality in this population is in excess of 50%. Thus, considerable effort has been expended to develop techniques to prevent ARF or to facilitate its resolution. Unfortunately, preventing the development of ARF in at-risk populations is an attractive but difficult goal. Well-powered studies have failed to demonstrate that drugs, such as low-dose dopamine, atrial natriuretic peptide or diuretics, can prevent onset or deterioration of renal function in the critically ill, and some studies have even suggested harm. The best advice to date is disappointingly empiric—avoids hypotension, dehydration, and exposure to nephrotoxins. Recently, pooled data from small studies suggest that NAC can reduce the incidence of ARF secondary to radio-contrast agents. Given its low cost and excellent side effect profile, it would seem prudent to provide NAC along with intravenous fluids to all patients with underlying renal insufficiency and those with diabetes or underlying cardiovascular or hepatic disease who are receiving intravenous radio contrast. Whether NAC can limit renal injury in other settings is a subject of ongoing study.

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