NO ADDED MORTALITY BENEFIT FROM CURRENT APPROACHES TO RENAL REPLACEMENT THERAPY IN ICU PATIENTS

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Disclosure: No potential conflict of interest.
Received: 05.03.14 **Accepted:** 12.05.15
Citation: EMJ Neph. 2014;1:76-82.

ABSTRACT

Hospital-acquired acute kidney injury (AKI), a common and harmful renal disorder, is an independent risk factor for short-term and long-term mortality particularly in critically ill patients. The management of this patient subpopulation remains supportive, with renal replacement therapy (RRT) indicated in severe renal failure. RRT prevents immediate death from lethal complications of advanced AKI, and - undoubtedly - reduces the mortality in AKI patients. The field of RRT has undergone remarkable changes to further improve the dismal short-term outcome. However, trials have failed to demonstrate an additional survival benefit of choice of modality or increased dose, or timing of RRT initiation if RRT is adequately performed. Clearly, AKI is not an isolated event but results in multiple negative effects on inflammation or coagulation and in multiple organ dysfunction. The underlying mechanisms are not amenable to current RRT. Thus, we should be realistic in our expectations of what dialysis and haemofiltration could accomplish; they are not renal replacement therapies in the true sense of the word, but only supportive systems. Prevention of AKI by better care, earlier anticipation of AKI by use of novel biomarkers and pharmacologic therapy of emergent AKI, and the introduction of bioreactor systems into clinical treatment of AKI may be future strategies to further improve the poor outcome of these patients.

Keywords: Acute kidney injury, renal replacement therapy, outcome.

INTRODUCTION

Acute kidney injury (AKI) is common in hospitalised patients, in particular in those admitted to the intensive care unit (ICU). AKI complicates the clinical course of approximately 40% of critically ill patients with higher rates in septic ICU patients compared to patients undergoing elective surgery.

Undoubtedly, hospitalised patients affected by AKI have a poor short and long-term prognosis. AKI is associated with significantly increased in-hospital mortality, prolonged length of ICU or hospital stay, longer dependence on mechanical ventilation, or non-recovery of renal function at discharge. Survivors may experience *de novo* development and progression of chronic kidney disease (CKD); they require frequent re-hospitalisations, experience impaired quality of life, need re-institution of dialysis for end-stage renal disease (ESRD), and show dismal long-term survival. Outcomes of hospital-acquired AKI are related directly to the severity of AKI (Risk, Injury, Failure, Loss of function, and End-stage renal disease [RIFLE] staging criteria).

In the absence of causative therapies for established AKI, its management remains supportive. Renal replacement therapy (RRT), using one or more of the modalities of dialysis or haemofiltration, is required in approximately 5% of all patients affected by AKI.[1,2]

MORTALITY OF CRITICALLY ILL PATIENTS WITH SEVERE AKI

The mortality of AKI due to acute tubular necrosis approached 100% during World War II. The introduction of haemodialysis during the Korean War improved mortality from about 90% to 50%. This

remains the best evidence to date that haemodialysis improves short-term outcome of critically ill patients with AKI.[3]

AKI-associated mortality is decreasing[4,5] but the outcome remains poor. In the literature, the mortality rate of patients with AKI plus three failing organs, and a sequential organ failure assessment (SOFA) cardiovascular score of 3 or 4 is 50% at 90 days, whereas 10 years ago it was 65%. Regarding non-septic AKI requiring RRT, the overall mortality can be as low as 40% at 90 days.

Patients die of AKI, not just simply with AKI. Even small changes in serum creatinine concentrations (<0.5 mg/dl) after cardiothoracic surgery are associated with a substantial increase in the risk of death.[6] A prospective multicentre cohort study[7] found that ICU patients with AKI requiring RRT, matched with ICU subjects for age and severity of illness, had a significantly higher hospital mortality. These results provide further evidence that AKI presents a specific and independent risk factor even under conditions of RRT.

Well-known complications of AKI are fluid overload, retention of uraemic toxins, and electrolyte abnormalities which need at least partial correction. New concepts argue that the development of AKI is the consequence of complex interactions between the actual insult and the subsequent activation of inflammation and coagulation cascades. Experimental models of AKI show that AKI instigates and multiplies cardio-pulmonary, hepatic, and neurologic dysfunction. Further studies provide evidence that AKI is associated with higher infection rates.[8-10]

CURRENT APPROACHES TO RRT

The aims of RRT for AKI are to maintain metabolic and volume homeostasis, and to prevent uraemic complications and dysfunction of vital organs during the acute illness until renal function recovers. These benefits must be balanced by potential harms, such as central venous access complications, infection, anticoagulation with heparin and its multiple untoward side-effects, depletion of electrolytes and micronutrients, incorrect dosing of antimicrobial drugs, hypotension, and aggravation of renal and systemic inflammatory effects by the components of the extracorporeal circuit.[11] The introduction of citrate has revolutionised anticoagulation for continuous renal replacement therapy (CRRT). Compared to heparin, citrate anticoagulation reduces the risk of bleeding and requirement for blood products in patients with or without coagulopathy. Regional citrate anticoagulation effectively prevents extracorporeal thrombosis and improves the delivery of RRT. The use of citrate may also be associated with less systemic inflammation.[12] In critically ill patients, different factors modify the elimination of drugs, particularly antibiotics, when CRRT or sustained low-efficiency dialysis (SLED) is performed. Altered pharmacokinetics of many antibiotics must be taken into account, and a modification of dosages is usually necessary to prevent underdosing.[13]

Choice of RRT Modality

RRT is increasingly performed as CRRT, as conventional intermittent haemodialysis (IHD), hybrid techniques (slow extended daily dialysis [SLEDD]), or prolonged intermittent renal replacement therapy (PIRRT), and rarely acute high volume peritoneal dialysis (PD).

CRRT is perceived to offer greater cardiovascular stability. However, IHD interventions, such as daily frequency, augmented duration, volumetric control of ultrafiltration, bicarbonate based dialysate, sodium modelling, ultrafiltration profiles, cooled dialysate, increased dialysate calcium, and biocompatible dialyser membranes, may lead to a reduction in intradialytic hypotensive episodes, and, thus, enable the safe treatment of almost all critically ill patients with AKI.[14]

Based on systematic reviews, there is no convincing evidence that CRRT is superior to IHD in terms of mortality.[15-19] These meta-analyses did not include the recently published monocentric Continuous Versus Intermittent Renal Replacement Therapy on the outcome of critically ill patients with acute renal failure (CONVINT) trial.[20] The authors of these randomised controlled trials (RCTs) observed no significant differences between daily IHD and continuous veno-venous haemofiltration (CVVHF); they concluded that IHD and CRRTs may be considered equivalent. The rate of comparison of CRRT and hybrid techniques (SLED) is low; very few prospective RCTs are done on SLED. In a randomised trial of 60 patients, continuous veno-venous haemodiafiltration (CVVHDF) was compared to 6-8 hours of SLED. There was no difference in ICU or 30-day mortality among treatment arms.[21] The RRT Study in ICU patients (a monocentric RCT) compared SLED with CVVH and observed similar outcome (90-day mortality) between 12-hour SLED

or 24-hour CVVH.[22] However, more data are needed to state that SLED is equivalent to CRRT. Moreover, both published RCTs have significant drawbacks such as a small number of participating patients and an insufficient statistical power to discriminate differences among treatment groups.[21,22]

Data comparing high volume PD to IHD or CRRT are scarce. One RCT compared daily IHD and high volume PD in 120 patients. High-dose continuous PD provided appropriate metabolic control and survival, while recovery of renal function is similar to daily IHD.[23] Another RCT compared high volume PD and extended daily haemodialysis, and found no evidence of a survival benefit.[24]

The recent Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI, recommend that CRRT and IHD are used as complementary therapies, with the suggestion that CRRT be used preferentially for haemodynamically instable patients and exclusively in AKI patients with brain injury or increased intracranial pressure resulting from intracranial haemorrhage or fulminate liver failure. The modality chosen should be guided by the individual patient's clinical status, medical and nursing expertise, and the availability of RRT modes. However, both the frequency and duration of IHD should be adjusted to minimise episodes of intradialytic hypotension by avoiding high ultrafiltration rates.[25]

Choice of RRT Modality and Dialysis Dependence after AKI

Development of *de novo* progressive CKD, acceleration of pre-existing CKD, non-recovery of renal function, or ESRD requiring chronic dialysis are associated with higher long-term mortality. Multiple observational studies, including a recently published retrospective cohort study,[26] but none of several prospective RCTs, indicated that ICU AKI patients initially treated with intermittent rather than continuous RRT are more likely to become dialysis dependent. A retrospective analysis of 145 septic AKI patients who received RRT with CVVHF or extended daily haemofiltration (EDHF) found that patients who underwent CVVHF had significantly improved renal recovery independent of clinically relevant variables, but had similar 60-day all-cause mortality rates.[27] Also, the pooled database and subsequent analysis of the Randomised Evaluation of Normal Versus Augmented Level Replacement Therapy (RENAL) and the Veterans Affairs/National Institutes of Health (VA/NIH) trials showed impressive results regarding renal recovery when CRRT was started first (instead of IHD) in haemodynamically unstable patients.[28]

A Cochrane systematic review comparing IHD with CRRT found similar hospital mortality, ICU mortality, length of hospital stay, and renal recovery in critically ill patients. It is important to keep in mind that only three small RCTs, but none of the observational studies, were included in this part of the analysis.[15] A recently published systematic review and meta-analysis included 23 studies (7 RCTs, 16 observational studies). Pooled analyses of the RCTs demonstrated no significant difference in dialysis dependence rates between the modalities, but pooled analyses of the observational studies showed that patients who initially received IRRT had a 2-fold increased risk of dialysis dependence compared with CRRT. However, the latest meta-analyses have important limitations. The adjusted analyses found a higher rate of dialysis dependence in five observational studies and no difference in two observational studies. There were severe limitations in the observational studies (study design, lack of baseline renal function, cause and severity of AKI, unknown distribution of non-renal comorbid disease and CKD at baseline, days on RRT and prescription of IHD, and number of hypotensive episodes). The investigators acknowledged that their findings rely exclusively on data from observational studies, which might be associated with allocation bias.[29] Given the human and public health implications of better AKI outcomes, large RCTs, focusing on renal recovery after AKI, are needed to fully understand the potential effects of initial modality choice on subsequent dialysis dependence and long-term mortality.

TIMING OF RRT IN CRITICALLY ILL PATIENTS WITH AKI

Classical indications for RRT initiation in ICU patients include uraemic symptoms and signs, hyperkalaemia refractory to medical management, volume overload unresponsive to fluid restriction and diuretics, as well as metabolic acidosis that is severe or accompanied by volume overload, precluding adequate bicarbonate therapy. In this situation, RRT is the rescue therapy of immediately lethal complications of severe AKI. Current practice, however, is to initiate RRT early, although RCTs have not been able to document significant benefits of prophylactic dialysis.[16]

In the absence of robust predictive markers of renal functional recovery, there is no commonly accepted definition for the optimal timing of initiating RRT, and indications remain controversial.

Numerous studies have compared early and late initiation of RRT in critically ill patients with AKI (RIFLE Stage 3 or Acute Kidney Injury Network [AKIN] Stage 3). The majority have been retrospective cohort analyses or prospective observational studies and have used a variety of definitions for 'early' or 'late'. To explore the optimal timing for initiation of RRT different parameters were used, including arbitrary cut-offs for serum creatinine, serum urea, urine output, fluid balance, hyperkalaemia, and time from ICU admission or time after onset of AKI. The data obtained are conflicting. One small RCT indicated that of the 28 CRRT patients treated per protocol, 12 patients in the early group (86%) were alive at 2 weeks compared with only 2 patients (14%) in the late group.[30] The two other RCTs found no significant differences between early or late therapy.[31,32] 208 patients with progressively worsening community-acquired AKI participated in a recently published RCT. Early IHD was initiated when serum urea nitrogen and/or creatinine levels increased to 70 and 7 mg/dl, respectively. Usual start patients received IHD when clinically indicated. 27 (13%) patients recovered kidney function before even receiving RRT. Primary outcome data (in-hospital mortality and dialysis dependence at 3 months) did not support early initiation of IHD in community-acquired AKI.[32]

Three meta-analyses concluded that earlier institution of CRRT or IHD in critically ill patients may be associated with a survival benefit.[33-35] However, the studies were heterogeneous and of variable quality and size with few RCTs. The majority of retrospective analyses used conventional parameters of renal function. However, serum levels of creatinine or urea, as well as urine output, depend on multiple non-renal factors as well. The criterion 'duration of admission to ICU to start of RRT' can only be determined retrospectively; the exact duration of AKI remains often speculative, and the diagnosis of AKI is often delayed or even early AKI is missed when the current gold standard 'serum creatinine' is used. Furthermore, the vast majority of primary studies restricted their analyses to patients who received RRT. However, patients who do not receive early RRT can follow different paths. They may need late initiation of RRT, they may die before initiation of dialysis, or they may recover kidney function. It cannot be excluded that more patients with less severe AKI (less than RIFLE Stage 3) received early RRT and it may be possible that the severity of the underlying illness and patient characteristics were different from those of patients in whom RRT was delayed. Also, earlier initiation of RRT may have been prompted by volume overload or life-threatening electrolyte disturbances, whereas progressive uraemia and distant organ dysfunctions may trigger a late start of RRT.

A recent multicentre retrospective study enrolled 648 ICU patients with post-surgical AKI. The initiation of RRT was categorised according to the time between ICU admission and start of RRT as early (less than 1 day), intermediate (2-3 days), and late (4 or more days). Estimated probability of death and in-hospital mortality rates followed 'U curves', suggesting that very early and late initiation of RRT may equally increase mortality.[36]

Taken together, the additional effect of timing the initiation of RRT on survival of patients with severe AKI is yet to be investigated in large RCTs. There is an urgent need to clarify whether subgroups of critically ill patients with septic AKI or cardiogenic shock benefit from an earlier commencement of RRT. Future trials should use a panel of novel biomarkers to define early and late initiation of RRT.

The KDIGO Clinical Practice Guidelines recommend[25] the decision to initiate RRT should be based on the clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests rather than single blood urea nitrogen or creatinine levels. The initiation of RRT may be deferred if the underlying clinical condition is improving. There may be patients with a futile prognosis in whom RRT would not be appropriate.

INTENSITY OF RRT

Clinical trials of the intensity of RRT for AKI have produced conflicting results. There is no consensus regarding the optimal intensity of RRT to address the high mortality of critically ill patients with AKI requiring RRT. Traditionally, in studies with ICU patients, the dosage of RRT has been assessed by variants of Kt/V urea in dialysis based modalities, all of which have limitations. Due to the difficulty in assessing the volume of distribution of urea, the delivered dosage of IHD can be markedly lower than that prescribed and is not routinely measured in

clinical practice. The weight-adjusted effluent flow rate is used as surrogate for convective therapies. However, any assessment of RRT adequacy based solely on small solute clearance remains incomplete and neglects fluid balance and removal of middle and large-sized molecules.

Although studies assessing the effect of RRT intensity on mortality of AKI patients have been conducted since 1975, there is a paucity of data regarding adequate dosage of RRT to be delivered for AKI, particularly for IHD or SLED. The majority of trials published before 2008 clearly favoured more intensive therapy, whereas trials published after 2008 showed more intensive RRT not to be more effective than less intensive regimens. This difference is probably due to study design (single centre versus multicentre), patient characteristics, and the actual RRT dosages delivered.

Two large-scale multicentre trials of higher versus standard dose RRT in critically ill patients with AKI, the VA/NIH trial,[37] and the RENAL trial,[38] found no improvement in clinical outcomes with the delivery of a higher intensity dose, including endpoints such as survival or renal recovery. Recent meta-analyses are similarly negative, showing no improvement in overall outcome or in patient subsets (septic versus non-septic) with higher doses of RRT.[39,40] A minimum delivered dose of at least 20-25 ml/kg/hour for CRRT and a single pool Kt/V urea of 1.2-1.4 for IHD thrice-weekly appears adequate for many critically ill AKI patients.[25] It is accepted that hypercatabolic or volume overloaded patients may require higher doses or frequencies of RRT. Given the well-known discrepancies between prescribed and delivered doses in RRT in the acute setting, prescribing a modestly higher dose of therapy may be necessary to achieve target doses.

HIGH VOLUME HAEMOFILTRATION FOR SEPTIC AKI

High volume haemofiltration effluent rates >50 ml/kg/hour were believed to improve outcomes in critically ill patients with sepsis or septic shock. However, two recent meta-analyses including three or four RCTs, respectively, did not show any meaningful difference in early mortality between high volume and standard volume haemofiltration. There is insufficient evidence for a therapeutic benefit for the routine use of high volume haemofiltration in septic AKI.[41,42]

Biocompatibility of Haemodialysis Membranes and Outcome of AKI

The effect of bio-incompatibility of haemodialysis membranes on mortality in AKI has been the subject of intense and industry-driven debate, with some - but not all - studies reporting a lower risk of death among patients dialysed with biocompatible membranes compared to bio-incompatible membranes. Two meta-analyses suggested a survival advantage for synthetic membranes over unsubstituted cellulose (cuprophane) membranes.[43,44] As cuprophane membranes have been phased out over time and the price difference between synthetic and modified cellulose membranes is negligible, the impact of membrane choice on patient outcome has become somewhat passé.

CONCLUSIONS

Mortality associated with severe AKI remains unacceptably high, in spite of a number of new advances in RRT technology and approaches to RRT. Although it has been argued that RRT is not yet fully optimised, further adjustments of RRT in ICU AKI may have little impact on overall mortality. In the setting of multi-organ failure, we should be realistic in our expectations of what dialysis and haemofiltration can accomplish. Cell therapy devices are currently developed to replace the filtrative, metabolic, and endocrinologic functions of the human kidneys lost in AKI.[45] The bioartificial kidney, which incorporates a haemofilter with tubular cell lines, may be particularly promising in this regard.

The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) 2009 report on AKI, 'adding insult to injury', identified deficiencies in care in 50% of hospitalised cases, including failures in AKI prevention, recognition, therapy, and timely access to specialised services. 30% of cases of AKI were judged to be preventable.[46] Early identification of AKI with novel candidate biomarkers may be an important step in improving outcome. These biomarkers help not only in the early detection of AKI before the onset of a rise in serum creatinine, but also in the differential diagnosis of the condition.[47]

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