Review Article

Current practice of conventional intermittent hemodialysis for acute kidney injury

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ABSTRACT

The use of conventional intermittent hemodialysis (IHD) represents a mainstay of supportive care of patients with acute kidney injury (AKI). However, a number of fundamental questions regarding the optimal management of IHD remain unanswered after more than six decades of renal replacement therapy (RRT). This review summarizes current evidence regarding the timing of initiation of intermittent hemodialysis, the comparative outcomes (mortality and recovery of renal function), the prescription of the intensity of this therapy and discontinuation of dialysis. The way conventional IHD is performed has an impact on the outcome of sick patients with AKI. The value of regular education and training of those who provide IHD cannot be emphasized enough. However, we must be realistic in our expectations that no mode of RRT *per se* will substantially alter the excessive mortality of critically ill-patients with AKI.

Key words: Acute kidney injury, intermittent hemodialysis, standard of care

Introduction

Acute kidney injury (AKI) (previously termed acute renal failure) is characterized by the rapid and sustained reduction of glomerular filtration rate resulting in the retention of nitrogenous (creatinine and urea) and non-nitrogenous metabolic waste products and dysregulation of body fluid volume status, electrolyte and acid-base homeostasis. AKI is defined by the recent Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI,[1] by any of the following: (a) An increase of serum creatinine by more than 0.3 mg/dl within 48 h, (b) an increase of serum creatinine to 1.5 times of baseline within the prior 7 days, or (c) an urine volume of less than 0.5 ml/kg/h for 6 h. Thus, the diagnosis of AKI by functional instead of structural biomarkers has essentially not changed over a century. However, the current paradigm for diagnosing early AKI largely by the detection of changes in serum creatinine or urine output remains susceptible both to delays in the diagnosis of this renal syndrome, but also to missing small, but relevant changes of glomerular filtration rate.

Hospital-acquired AKI may develop in a wide variety of clinical settings, including ambulatory out-patients, general ward patients and in particular, critically ill-patients for whom AKI represents a common complication of both underlying illness and its treatment. Hospital-acquired AKI is common and its overall incidence is increasing in developed countries. This reflects increased acuity of underlying diseases, more aggressive radiologic, medical or surgical treatment of aged patients as well as increased detection of the renal disorder. Hospital-acquired AKI is a heterogeneous syndrome that arises predominantly secondary to ischemia, nephrotoxins and bacterial sepsis, but rarely from genuine acute renal diseases. In the intensive care unit (ICU), AKI manifests itself in the majority of patients as part of multiple organ failure.[2,3]

The renal syndrome AKI has a broad spectrum of clinical manifestations ranging from discrete acute tubular injury (detected by novel biomarkers only) to mild kidney injury and severe oligo-anuric acute kidney failure requiring renal replacement therapy (RRT). The recognition of the clinical relevance of all AKI manifestations resulted in the

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change in terminology from acute renal failure, for which the focus was limited to the most severe manifestation to AKI, with increased focus on small decrements in kidney function. Even the mild forms of AKI are independently associated with prolonged hospitalization, substantial health-care spending as well as high in-hospital mortality. Surviving patients are at high-risk for excess long-term mortality and development of *de novo* chronic kidney disease (CKD) or progression of pre-existent chronic renal failure.[4,5] Despite numerous advances in intensive care and renal replacement technologies, the acute mortality of critically ill-patients with AKI severe enough to start RRT is unacceptably high (40-60%) and the long-term survival extremely low (10-20%) at 10 years.[6]

Supportive Care of AKI Patients

In the absence of any effective pharmacologic therapy to delay progression of AKI or to speed up recovery of renal function, the management of these patients remains supportive, focusing on optimized fluid balance, preventing or treating electrolyte and acid-base disturbances, adjusting the dose of potentially nephrotoxic drugs or avoiding secondary hemodynamic and nephrotoxic kidney injury. RRT, often with more than one modality, is required in 4% of all patients with AKI.[7]

Modes of RRT: The Place of Conventional Intermittent Hemodialysis

Current modalities of RRT for AKI include conventional IHD, continuous renal replacement therapy (CRRT), hybrid treatments (such as prolonged intermittent RRT) and high volume peritoneal dialysis. Controversy exists as to which is the optimal modality for patients with AKI. No RRT mode is ideal for all patients with AKI as they all have advantages and disadvantages. Several randomized controlled trials (RCTs) have compared IHD to CRRT, but randomized trials comparing peritoneal dialysis or sustained low-efficiency dialysis (SLED) with IHD are limited.

Three systematic reviews and meta-analyses concluded that there is no evidence that any single modality of RRT is associated with improved outcomes of patients with AKI.[8-10] The most inclusive meta-analysis by the Cochrane collaboration found similar hospital mortality, ICU mortality, length of stay and renal recovery in critically ill-patients treated with CRRT or IHD. However, most of the studies maximized hemodynamic tolerance of IHD compared with conventional IHD (augmented duration, daily frequency, positive sodium and negative thermal balance). Moreover, the high rate of crossover between the treatment modalities also complicates interpretation. Analyses have repeatedly suggested that the costs of CRRT are higher than that of IHD.

The recent KDIGO clinical practice guidelines for AKI recommend the use of IHD and CRRT as complementary therapies.[1] However, in patients with brain injury or increased intracranial pressure resulting from intracranial hemorrhage or fulminate liver failure IHD has been associated with a greater decrease in cerebral perfusion than CRRT. This may be the result of a decrease of mean arterial pressure or an increase of cerebral edema and intracranial pressure (dialysis disequilibrium) and may jeopardize neurologic recovery.

In current clinical practice, the choice of RRT is primarily based on the availability of and experience with a specific mode of RRT. Globally, the choice of RRT varies considerably between countries. CRRTs have become the most commonly used mode of RRT in critically ill-patients with AKI severe enough to require RRT. However, IHD remains the mainstay of supportive care of AKI world-wide, when appropriately modified. Hemodynamic instability with intermittent RRT may be decreased by using variable dialysate sodium profiles (160-140 meq/L), variable ultrafiltration rates, setting dialysate temperature to below 37°C combined with prolonged treatment time or altered frequency and enable safe treatment of critically ill-patients with AKI.[11] Transition between CRRT and IHD is frequent, mostly determined by improved hemodynamic status of the patient or occurrence of coagulation problems. Undisputedly, IHD is the mode of choice in all mobile patients with AKI.

Indications for Start of IHD

The timely commencement of RRT in AKI is fundamental to achieve treatment goals, namely, providing solute clearance and removal of excess fluid while awaiting recovery of kidney function. Emergency initiation of RRT in AKI is performed in response to these classical indications: Volume overload unresponsive to diuretic therapy, electrolyte and acid base disturbances refractory to medical management and overt uremic manifestations, such as pericarditis or encephalopathy. RRT can be characterized in this situation as rescue therapy in which commencement of treatment forestalls imminent death. More often however, RRT is initiated preemptively, well before the development of these complications, in patients with severe AKI in whom imminent recovery of sufficient renal function is unlikely. Prophylactic RRT describes the initiation of RRT before nitrogenous waste products

reach some arbitrary predefined blood concentrations, regardless of other indications. However, there is no evidence that prophylactic RRT might be associated with a survival benefit.[12]

The uncertainty regarding the optimal timing for starting RRT in AKI patients is derived largely from the inability to predict if and when established AKI will recover. In the absence of robust predictive markers (novel biomarkers) earlier initiation of RRT increases the numerous risks of unnecessary treatment in patients who might eventually recovery sufficient renal function if managed conservatively.

The lack of consensus on accepted non-lethal indications for timing of RRT in AKI has led to substantial variability in the timing of RRT across the world. Data from the randomized evaluation of normal versus augmented level replacement therapy study, which compared two different doses of CRRT in critically ill-patients with AKI, showed that 60% of patients had severe edema when RRT was started and 40-50% of patients had either a serum creatinine greater than 3.4 mg/dl or serum urea greater than 70 mg/dl. 8% of patients were hyperkalemic (serum potassium greater than 6.5 mol/L) at the time of the first RRT session.[13] Of note, only 37% of patients participating in another RCT were oliguric, indicating predominantly metabolic disturbances in this patient population.[14] There is concern that differences in the initiation criteria for RRT might have influenced the outcome in trials comparing different doses of CRRT.

In a recent survey of Canadian nephrologists and critical care physicians,[15] hyperkalemia and volume expansion were strong factors for the decision when to initiate RRT for AKI while the absolute concentrations for serum creatinine and urea influenced decision making for 57% and 59% of the respondents, respectively. The survey highlighted other factors that influence the decision to start RRT, namely the time of the day when laboratory results become available, patient age and comorbid conditions, urine output following diuretic administration and the specialty of the attending physician. Moreover, in a large and sparsely populated country like Canada, the actual timing of RRT initiation in relation to the development of AKI may be influenced by potential delays in arranging patient transfer to centers that offer RRT.

In general, there is a tendency to avoid RRT as long as possible in non-critically ill-normuric AKI patients, a thought process that reflects decisions made for patients with CKD stage V. However, the situation is very different for ICU patients with AKI were RRT is generally viewed as type of organ support rather than a detoxification procedure aimed as an adjunct to enhance kidney function, modify fluid balance and allow parenteral nutritional support.

There is no doubt that the benefits of early initiation of RRT must be weighed against potential harms. Potential benefits of early initiation of RRT are more rapid metabolic/uremic control and more effective prevention and management of volume overload. The major counter argument is that early RRT might subject sick patients who would recover renal function with conservative treatment alone to the potential risks of RRT. The well-known risks of RRT include hemodynamic instability with hypotensive episodes and arrhythmia, induction of the systemic inflammatory syndrome and infectious complications of the vascular access. There is some concern that RRT particularly IHD may compromise recovery of renal function and increase the progression of CKD. By contrast, late RRT avoids treatment in patients with potentially recoverable AKI, but increases the risk of fluid overload or uremic complications.

During the last two decades, there have been multiple studies comparing early and late commencement of RRT. The majority of the published reports has been retrospective cohort studies or prospective observational studies and has used a wide variety of definitions for early and late initiation of RRT. These studies have evaluated various arbitrary cut-offs for serum creatinine, serum urea or urine output, fluid balance, time from ICU admission or duration of AKI. There are only two RCTs containing data on timing of RRT in critically ill-adult-patients with AKI Bouman *et al.*,[16] randomized 106 ICU patients who were oliguric to three groups: Early high volume continuous veno-venous hemofiltration (CVVH), early low-volume CVVH and late low-volume CVVH. The differentiation between early and late RRT was based on urine output, creatinine clearance, hyperkalemia and presence of pulmonary edema. There were no differences in 28-day mortality or recovery of renal function. Interestingly, in the late CVVH arm, four patients recovered renal function spontaneously and two patients died before the criteria for initiation of RRT were reached. The authors concluded that there was no benefit with early CVVH. Sugahara and Suzuki,[17] evaluated the role of timing of continuous hemodialysis (CHD) in 28 patients with AKI post-cardiac surgery. Fourteen patients were started on CHD when their urine volume decreased below 30 ml/h for 3 h. In the late CHD arm, RRT was delayed until urine output had fallen below 20 ml/h for 2 h. Survival

was significantly better in the group of patients who started RRT earlier. There were no differences between the two study arms with respect to age, gender, acute physiology and chronic health evaluation II score and serum creatinine.

Three meta-analyses concluded that earlier institution of CRRT or IHD in critically ill-patients might be associated with a survival benefit.[18-20] However, the studies were heterogeneous and of variable quality with a paucity of randomized trials. It is important to recognize the number of critical methodological flaws affecting the majority of studies evaluating optimal timing of RRT. First, despite the impression that early RRT may be superior; the data published by the primary studies are conflicting. The majority of the studies are retrospective analyses with different biochemical cut-offs. However, serum levels of creatinine and urea, as well as urine outputs depend not only on renal function, but also on non-renal factors. The RIFLE[21] and acute kidney injury network,[22] classifications are scoring systems to grade prognosis of AKI, but they were never intended to predict the need for RRT. The criterion "duration of admission to ICU to start of RRT" can only be determined retrospectively. The exact duration of AKI remains often speculative. The diagnosis of AKI may be delayed or even early AKI missed when the gold standard "change in serum creatinine" is used. Second, the vast majority of the 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 may recovery kidney function without requiring RRT. Limiting the comparisons to patients treated earlier or late neglects the large number of patients who meet criteria for early treatment, but never undergo dialysis. Third, it cannot be excluded that patients with less severe AKI were included in the early group and it may be possible that patients of the early group were different from patients in whom RRT was delayed. Earlier initiation of RRT may have been prompted by volume overload and/or life-threatening electrolyte disturbances, whereas progressive uremia may have been the trigger for the late start of RRT. Finally, the tension between potential benefits of earlier treatment and risks of unnecessary treatment remains central to the ongoing debate on the timing of RRT. In a single center retrospective study of 5383 critically ill-patients, Hoste *et al*.,[23] found that of those developing RIFLE class R, 56% progressed to either class I or F and of those developing RIFLE class I, 36% progressed to RIFLE class F. Patients achieving RIFLE class F had a far worse outcome, but only 14.2% received RRT. This shows that there is currently no predictive model for whom to treat or not to treat by RRT.

Interestingly, a recent multicenter retrospective observational study enrolled 648 ICU patients with post-surgical AKI requiring RRT. These patients were categorized according to the period of time between ICU admission and RRT initiation as the early (less than 1 day), intermediate (2-3 days) and late (4 or more days) group. Both estimated probability of death and the in-hospital mortality rates of these followed U-curves,[24] suggesting that very early and late initiation of RRT may equally increase mortality.

In the absence of reliable markers predicting recovery of renal function, the decision to initiate RRT should be based on the clinical context of the AKI patient, the presence of conditions that can be modified with RRT and trends of laboratory tests rather than single blood urea nitrogen (BUN) or creatinine thresholds alone. 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 and where withholding RRT constitutes good end-of-life care.

Dosing of IHD in AKI

The judgment and awareness of how a particular therapeutic regimen should be prescribed and actually be delivered is essential for good medical practice. However, recent surveys have shown that a disappointingly low number of nephrologists/intensivists report being aware of the importance of calculating RRT dose in AKI and even more importantly, not calculating RRT dose in AKI in actual practice.[25,26]

Quantification of the delivery of dialysis is based most commonly on clearance of urea as a surrogate for low-molecular weight uremic toxins. IHD dose is quantified either by urea reduction rate or fractional urea clearance per treatment, expressed as Kt/V urea. However, urea kinetic models have been validated exclusively for maintenance hemodialysis patients with end-stage renal disease (ESRD). There are multiple limitations to their use in quantifying acute IHD because a number of the fundamental assumptions underlying these calculations are violated in AKI. Unlike patients with ESRD undergoing IHD, critically ill-patients with AKI are often hypercatabolic and in negative nitrogen balance. In addition, alterations in regional blood flow in patients with cardiovascular instability can result in disequilibrium in urea distribution between body fluid

compartments, invalidating standard single pool models. Finally, the volume of distribution is often expanded in AKI, exceeding total body water calculations based on anthropometric parameters. Despite these limitations and in the absence of simple superior metrics, Kt/V urea has been satisfactorily used for dose quantification in critically ill-patients receiving acute IHD.[27] Because urea removal during the IHD is proportional to blood urea concentrations, the absolute rate of removal might be greater at the start of treatment and decrease over time. Thus, the effective weekly dose of therapy must be calculated from all sessions and cannot be extrapolated.

Only two adequately designed and executed RCTs tested different RRT doses in critically ill-patients. There have been no prospective studies comparing doses of IHD on a fixed dialysis schedule in patients with AKI. Our single center study,[28] has evaluated the impact of increased frequency of IHD treatments with a pre-treatment dose held constant. We assigned 160 critically ill-patients in an alternating fashion to receive conventional IHD (mean duration of session 3.3 h, mean blood flow rate 245 ml/min, dialysate flow rate fixed at 500 ml/min) on either a daily or every otherday schedule. IHD was prescribed with a target Kt/V urea of 1.2/session, which was common practice at this time, derived from chronic dialysis patients. However, actual delivered Kt/V urea was 0.93. Mortality 14 days after the last dialysis session was significantly lower in patients who received daily compared with alternate day IHD. Recovery of kidney function, defined as dialysis independence also occurred more rapidly with daily than with alternate day IHD. Given the higher rate of uremic complications, including sepsis, gastrointestinal bleeding and alterations in mental status, observed in the alternate day IHD arm, it has been suggested that this study showed the hazards associated with underdosing of therapy rather than a benefit of an augmented dose of IHD therapy. Nonetheless, these data indicated that the prudent approach is to prescribe more frequent dialysis for ICU patients treated with IHD, to optimize dose delivery, fluid balance and outcome. In contrast, the Veterans Administration/National Institutes of Health Acute Renal Failure Trial Network (VA/NIH ATN) study,[29] used a strategy that allowed patients to switch between RRT modalities as their hemodynamic status changed over time. In the ATN study, 1124 critically ill-patients with AKI were randomized to either an intensive or less intensive strategy. In both treatment arms, RRT was provided as IHD when patients were hemodynamically stable and as either venovenous hemodiafiltration or SLED when hemodynamically unstable. In the intensive strategy, IHD and SLED were provided on a 6-times weekly schedule with a target Kt/V Urea of 1.2-1.4. In the less intensive arm, IHD and SLED were provided on a 3 times weekly schedule with the same target Kt/V urea per treatment. 60-day all-cause mortality did not differ significantly between the intensive – therapy IHD arm and the less intensive IHD therapy arm. However, given the controversies in dose comparison between RRT modalities and the use of SLED in the IHD group, the ATN trial might best be described within current US practice rather than a direct test of a dose – survival response for critically ill-patients with AKI. Furthermore, 65% of patients had received one session of RRT for up to 24 h before randomization, but the net fluid balance of these patients was positive.[30] Third, the ATN study provided a dose of IHD, which exceeded that in usual care with conventional IHD. The performance characteristics of the less intensive IHD included a median duration of the session of 4 h, a mean blood flow rate of 360 ml/l and a dialysate flow rate of 720 ml/min. However, only 68% of the participating patients received the targeted dose. From both trials it may be concluded, that underdosing of RRT, when extrapolating dosing from the chronic dialysis setting, should be avoided and that the optimal recommended dose is yet unclear.

The KDIGO clinical practice guidelines for AKI recommend a delivered Kt/V urea of 3.9/week when using IHD. Providing higher doses of RRT is not associated with improved clinical outcome of ICU patients with AKI.[31,32] No study investigated the effects of tapering of the delivered dose both in critically ill-patients or non-critically ill-patients with AKI. It could be envisaged that application of initial high doses followed by a standard dose may decrease the time period during which homeostasis is severely disturbed.[33]

Discontinuation of IHD in AKI

Many patients with AKI recover sufficient kidney function to be independent of RRT, but criteria for stopping RRT have received little attention. The decision whether or when to stop IHD in patients with AKI needs to consider whether the improvement in kidney function is adequate to meet demands and consider the improvement of the disorder that precipitated AKI and prompted the start of RRT.

Assessment of kidney function during RRT depends upon the modality used. In IHD, the fluctuations of dialyzable solute levels particularly the post-treatment rebound of nitrogenous waste products prevent achieving a steady state and exclude exact measurements of (24 h) clearance. Native kidney function can only be assessed

during the interdialytic period by measuring urine volume, urinary excretion of creatinine and changes in serum creatinine and/or BUN values, but the latter can also be influenced by non-renal factors. One small study (published in abstract form) suggested that a creatinine clearance (measured over 24 h) greater than 15 ml/min was associated with successful termination of CRRT, defined as the absence of CRRT requirement for at least 2 weeks.[34] Recovery of renal function was defined by the investigators of the VA/ATN trial on the basis of creatinine clearance, measured with the use of 6 h timed urine collections when urine flow increased to more than 20 ml/h or when there was a spontaneous fall in the serum creatinine level. RRT was discontinued if the creatinine clearance was greater than 20 ml/min.[29] On the other hand, urine output seems to be a very important predictor of successful discontinuation of RRT. A *post hoc* analysis from an international multicenter study found that urine output was the most important predictor of successful sustained discontinuation. A total of 529 patients of 1006 ICU patients survived the initial period of CRRT, 313 were successfully removed from RRT, whereas 216 patients needed "repeat CRRT" within 7 days of discontinuation. Patients with a urine production of more than 400 ml/day without diuretics or more than 2300 ml/day with diuretics before RRT was stopped had a greater than 80% chance of successful discontinuation of RRT.[35] Wu *et al*.,[36] focused on risk factors for redialysis in 94 post-surgical patients with AKI for successful discontinuation of RRT. The patient group, which failed weaning from IHD had a mean urine output of 600 ml/min compared with 1400 ml/day in the successful group.

Whether or not too early discontinuation of RRT with the subsequent requirement of reinstitution is by itself harmful - as suggested by a few retrospective observational studies – has not been properly investigated.

The KDIGO clinical practice guidelines for AKI,[1] recommend discontinuation of RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patients' needs or because RRT is no longer consistent with the goals of care (no evidence level). Diuretics should not be used to enhance kidney function recovery.

IHD and Dialysis Dependence After AKI

CRRT and IHD achieve a satisfactory degree of metabolic and fluid control and to date; neither modality has been found superior in terms of mortality. The burden of *de novo* CKD and progression to ESRD is high in survivors of an episode of AKI requiring RRT. Whether or not choice of RRT modality may affect renal recovery and if so, patients treated with IHD might have higher rates of dialysis dependence compared with those treated with CRRT is subject of a never ending debate. The recent systematic review and meta-analysis by Schneider *et al*.,[37] included 23 studies, seven RCTs and 16 observational studies. Pooled analyses of RCTs showed no difference in the rate of dialysis dependence among survivors confirming two previous meta-analyses of RCTs.[8-10] By contrast, pooled analyses of observational studies suggested a higher rate of dialysis dependence among survivors who initially received IHD as compared with CRRT. The authors concluded that among AKI survivors, initial IHD might be associated with higher rates of dialysis dependence.[37] The association between IHD and increased dialysis dependence seems physiologically plausible, but CRRT may often be associated with hypotensive episodes, too.

However, the meta-analyses by Schneider *et al*.,[37] have important limitations. The adjusted analyses found a higher rate in five and no difference in two studies. The findings rely largely (exclusively?) on data from retrospective analyses or prospective observations utilizing IHD or SLED with a number of severe limitations (allocation bias, lack of confounders, exclusion of CKD by clearance measurements or urinalysis particularly microalbuminuria).

Currently, there is no solid evidence that adequately performed IHD might affect recovery of renal function. There is a need for large scale investigations with a detailed nephrological follow-up of survivors.

Conclusions

IHD remains the leading modality of RRT for patients with AKI. Currently, there is no clear evidence that CRRT or IHD is a superior modality. CRRT and IHD should rather be considered as complementary or alternatives therapies. IHD should be initiated instantly, when life-threatening changes of severe AKI occur. The preemptive start of IHD should consider the broader clinical context, the presence of conditions that can be modified by IHD and trends in laboratory tests. The dose of RRT to be delivered should be prescribed before the commencement of each IHD session and the actual delivered dose should be measured in order to adjust the prescription, when necessary. Conventional IHD may be associated with underdosing when provided every other day. Current knowledge seems to favor a delivered Kt/V urea of 3.9/week at least for

initial IHD therapy for critically ill-patients with AKI. An improvement in the patient's clinical condition and a significant increase in urine output associated with a spontaneous decrease in serum creatinine or a creatinine clearance of 20 ml/min would justify discontinuation of IHD under close monitoring. Survivors of severe AKI should be closely followed-up by a nephrologist.

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