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RENAL RECOVERY AFTER SEVERE ACUTE RENAL INJURY

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Abstract
Background: Recovery of renal function after acute renal injury is an important clinical determinant of patient morbidity and mortality. However, studies covering this field are scarce and nonhomogeneous.
Findings: Despite success in animal models, translation of current pharmacologic strategies to limit the extent of kidney dysfunction or to hasten renal recovery from acute kidney injury (AKI) in human studies has failed. Renal replacement therapy is the mainstay of supportive care in patients with AKI. However, its performance can have untoward effects that contribute to the prolongation of the course of AKI or impede the ultimate recovery of complete renal function. Use of biocompatible membranes, daily hemodialysis, advanced intermittent hemodialysis (IHD) technology or continuous RRT (CRRT) have been coupled with shortened renal recovery after AKI. Rate of renal recovery to RRT independence is variable when judged at hospital discharge. The frequency of end-stage renal disease in survivors from AKI is highest in severe acute parenchymal renal disease and lowest in acute tubular necrosis (ATN). Renal recovery is less likely in patients with preexisting renal disease. Renal recovery at hospital discharge may underestimate the true rate of renal recovery. The overwhelming majority of patients (more than 85 %) with severe ATN precipitating on normal renal function recover and maintain complete renal function or any degree of chronic renal functional impairment within 6–12 months after AKI. Partial or nonrecovery of renal function represents an independent predictor of long-term mortality for survivors from AKI. Re-need for RRT occurs in a small portion of survivors of severe ATN (less than 5%).
Conclusion: Severe AKI necessitating RRT should no longer simply be viewed as just an acute reversible complication of critical illness or short-term illness. Persistent reduction in renal function will exhibit independent effects on patient survival that extends well beyond discharge from the hospital.

Key words: Renal recovery, outcome, acute kidney dysfunction

INTRODUCTION

Hospital-acquired acute kidney injury (AKI) comprises a family of heterologous syndromes with multiple aetiologies, a wide range of severity, and a heterogeneous clinical course. AKI is common in medical and surgical hospitalized patients, especially among the critically ill and severely injured. The incidence of hospital-acquired AKI is steadily increasing [1, 2, 3]. This increase is multifactorial, and is related to an aging population with a high burden of co-morbid diseases, to the increasing severity of illnesses necessitating acute hospitalization, and to the high prevalence of nephrotoxic exposure or major surgical procedures performed in this population. AKI that is severe enough to require renal replacement therapy occurs in 5 to 6 % among intensive care unit (ICU) patients [4].

With changes in the demographic characteristics of hospitalized patients, the spectrum of causes of AKI has dramatically altered. AKI rarely occurs as single organ failure, but often develops as part of the multiple organ dysfunction syndrome. Acute tubular necrosis (ATN), the most severe form of AKI, occurs in 70 to 100 % of cases in ICU patients. Development of severe ATN complicates acute critical illness and constitutes a major barrier for recovery of critically ill patients.

Recovery of renal function after an episode of severe ATN is now identified as an important clinical outcome. Failure to recover complete renal function can negatively influence the health status and quality of life of these patients. Furthermore, provision of outpatient renal replacement therapies for end-stage renal disease, secondary to AKI, is associated with considerable healthcare costs. Despite many patients with AKI being treated in the ICUs and the high expenditure incurred on these patients, relatively little is known on short- and long-term renal recovery.

DEFINITION OF RENAL RECOVERY

The Acute Dialysis Quality Initiative has published a consensus definition for acute renal failure that includes provisions for defining renal recovery [5]. Complete renal recovery was defined as the return of kidney function to pre-ARF baseline levels. Recovery may be defined as partial if there is a persistent change in the baseline creatinine. Patients who require Renal Replacement Therapy (RRT) for more than 4 weeks suffer persistent loss of acute renal function, which is classified as acute renal failure (ARF), whereas those patients who remain dependent on RRT at 3 months would be defined as having progressed to end-stage kidney disease (definitive loss).This definition is both

disease- and patient-orientated, and is based on gradations in recovery of renal function.

Mechanisms that May Alter the Course of AKI or Impede Renal Recovery

Renal replacement therapy is the mainstay of supportive care in patients with severe AKI. However, its performance can have untoward effects that contribute to the prolongation of renal failure or impede the ultimate recovery of complete renal function.

Table 1. Interventions to improve renal recovery during established AKI.

Intervention:
Renal replacement therapy
Biocompatibility of dialyzer membrane
Higher dose (frequency) prescription of IHD
Advanced Technology: volumetrically controlled ultrafiltration, sodium profile, high calcium concentration, cooling of dialysate, bicarbonate-based ultrapure dialysate
Mode of RRT: continuous versus intermittent techniques

A major mechanism by which RRT is postulated to delay renal recovery relates to bio incompatibility of the dialyser membrane. The interaction of patient's blood with surfaces of foreign materials, in particular the dialyser membrane can cause inflammation by activating leukocytes and the release of humoral mediators resulting in renal parenchymal injury. The intensities of such responses are greatest with unsubstituted cellulose (cuprophane) membranes and lowest with synthetic polymer-derived membranes. Studies in experimental animals with ARF have shown that hemodialysis with cuprophane membranes (but not with more compatible membranes) can lead to neutrophilic infiltration into the kidney (and other tissues) and delayed recovery. These findings may be also applicable to human AKI as some, but not all, prospective randomized trials have shown that the survival rate of critically ill patients and the rate of recovery of renal function from AKI were significantly higher and that recovery occurred earlier when hemodialysis was performed with biocompatible rather than bioincompatible curophane membranes. Numerous potential reasons for this disparity have been proposed, including issues of study design (randomized vs. nonrandomized, prospective vs. retrospective), variable definition of biocompatibility (cuprophane or substituted cellulosic membrane), heterogeneous patient population, differences in timing, intensity and determination of RRT. In particular, most of the studies were focused primarily on intermittent hemodialysis (IHD) in noncritically ill patients, and defined recovery in terms of the absolute number of completed IHD sessions. However, given that the effect of biocompatible dialysis membranes is consistently beneficial and that differences in costs are no longer important, most nephrologists and intensivists favor the routine use of these membranes in the AKI setting [6].

Decreased renal perfusion as a result of hemodynamic instability is another commonly implicated mechanism for prolongation of renal injury. Renal biopsies in patients with prolonged AKI who are managed by using hemodialysis demonstrated regions of fresh tubular necrosis days to weeks after the initial inciting insult. Hypotension is a common complication of RRT, particularly in critically ill patients with underlying hemodynamic compromise. Multiple factors contribute to the development of hypotension during RRT including intravascular volume depletion, intercompartmental fluid shifts, and decreased cardiac output. Strategies to minimize the occurrence of hypotension during IHD therapy, such as monitoring of blood volume, sodium modelling, cooling of dialysate, minimizing the rate of ultrafiltration by longer or more frequent sessions, and the use of bicarbonate buffered ultrapure dialysate may have benefits with regard to recovery of renal function. In a comparison of daily IHD with every-other-day IHD, complete recovery of renal function was observed in all patients in the former treatment schedule. However, the time of recovery of renal function was shorter in the daily compared with the every-other-day treatment group. The mean ultrafiltration was significantly lower in the daily group compared with the volume in the every-other-day treatment group. Hypotension occurred in 5 ± 2% of treatment sessions in the daily group compared with 25 ± 5% of treatment sessions in the every-other-day treatment group. Thus, daily hemodialysis may mitigate ongoing renal injury by decreasing the ultrafiltration volume per treatment and the frequency of intradialytic hypotension [7]. Moreover, the clinical course of critically ill AKI patients who experienced multiple episodes of renal ischemia or nephrotoxin exposure during dialysis dependence was characterized by prolonged dialysis support [8].

Table 2. Factors associated with partial or nonrecovery of renal function after AKI.

Multiple (repeated) injuries to the kidneys
Cause of intrinsic renal dysfunction
Severity of AKI (RIFLE Classification)
Primary/secondary glomerulonephritis/ atheroembolism vs. ATN
Preexisting renal disease/dysfunction

Recovery of renal function has been evaluated as a secondary end-point in numerous trials comparing IHD to continuous RRT (CRRT). Despite the greater hemodynamic stability in the CRRT-treated patients, the majority of studies did not detect any difference in recovery of renal function or survival between groups.

Some nonrandomized studies suggest, however, that CRRT may result in greater recovery. Concerns have been identified in these studies with respect to study design, severity of illness at initiation of RRT and number of patients with preexisting kidney disease [9, 10, 11].

Failure of Current Pharmacologic Strategies for the Treatment of AKI

Despite success in various animal models, translation of current pharmacologic strategies to limit the extent of injury in AKI from animal to human studies has failed or possibly the studies are inconclusive. Among the available pharmacologic options for treatment of ATN, there is a remarkable lack of evidence supporting administration of loop diuretics, mannitol, and dopamine. Other drugs with theoretical value, specifically, atrial natriuretic peptide analogues, thyroxin, adenosine blockers, calcium antagonist's, insulin-like growth factor 1 or intensive insulin therapy have been insufficiently studied to recommend use. Other pharmacological options may arise in the future [12].

Experimental studies have shown that erythropoietin can alter the course of ARF, by exerting both cytoprotective and antiapoptotic effects, resulting in earlier regeneration of tubular epithelia and recovery. However, a retrospective cohort study reported the outcomes of 187 patients with AKI of whom 71 were administered erythropoietin. Recovery of renal function was similar in both groups. This study, however, was limited by its retrospective nature and by inadequate dosing and duration of treatment [13].

Factors Associated with Partial Recovery or Nonrecovery of Renal Function

Recovery to independence from RRT occurs at hospital discharge in approximately 68–100 % of critically ill patients [11, 14].

Cause and Severity of ARF

The frequency of end-stage renal disease (ESRD) in survivors varied in the series by Bhandari and Turney depending on the cause of intrinsic ARF. ESRD was highest in those with acute parenchymal disease and lowest in ARF secondary due to ATN [15].

The need for RRT has been estimated at 0–6 % in ARF secondary to ATN, if renal function prior to renal insult was normal [15]

Ali et al. tested the hypothesis that the Risk, Injury, Failure, Loss and End-Stage Kidney (RIFLE) classification predicts clinical outcomes. The RIFLE classification was useful for predicting both full recovery and RRT requirement [3]. Salmanullah and co-workers [16] retrospectively reviewed the relationship between serum creatinine and long-term renal function. Severity of AKI was classified as mild, moderate, and severe, with elevations in baseline creatinine of less than 50%, 50–300%, and over 300%, respectively. There were a total of 1,328 episodes of AKI in 916 patients that were suitable for analysis. Mild AKI on a substrate of normal or mildly abnormal renal function was resolved without long-term sequelae. However, a substantial number of those individuals with severe AKI had higher residual renal dysfunction after their bouts of AKI, regardless of whether the starting baselines were normal or abnormal.

Preexisting Renal Disease /Dysfunction

In recent studies of AKI in hospitalized patients, the prevalence of preexisting chronic kidney disease (CKD) has been estimated to be 30–35% [4,17,18]. Preexisting CKD or renal dysfunction appears to predispose to the development of dialysis-requiring AKI, and the effects of underlying CKD on renal outcomes following an episode of dialysis-requiring ATN are now well established.

When patients with CKD develop dialysis-requiring ATN, available data in critically ill patients suggest that renal recovery is less likely than in patients without CKD.

Eggers et al. reported at the Renal Week 2004 that both CKD status as well as age had a strong impact on the frequency of end-stage renal disease following AKI [19]. Compared with 28.2% of patients with preexisting CKD, only 7.6% of patients with normal renal function prior to AKI progressed to end-stage renal disease after 3 years. Within this time span, 48% of patients older than 85 years had end-stage renal disease as against 11.1% of patients who were younger than 65 years, suggesting that older patients more often had preexisting kidney disease.

Whether nonmodifiable factors such as age or gender are independently predictive of renal recovery remains uncertain. Our multivariate analysis failed to show age or sex as independent predictors of recovery at hospital discharge [14]. Bagshaw presented data of patients with a high burden of co-morbid illness at the time of the initiation of RRT who were less likely to recover to independence from RRT. However, baseline serum creatinine were not available in all patients and normal serum creatinine levels in critically ill, malnourished patients may mask renal dysfunction prior to precipitation of AKI [20].

Long-term Renal Outcome after AKI

The true value of intensive care should be determined by long-term rather than short-term outcome. Despite the many AKI patients treated in the ICU and the expenditure incurred on these patients, relatively little is known about the long-term renal outcome [21].

This contrasts with other specialities such as cardiology and oncology in which long-term outcomes have been extensively studied. The few studies reporting on long-term recovery have fundamental disparities in study design, study population, and timing for ascertainment of recovery prognosis.

Many of the studies only assessed renal recovery at ICU or hospital discharge and underestimated the true rate of renal recovery. The overwhelming majority of patients surviving the acute episode of AKI recover complete renal function or any degree of chronic functional impairment within 6–12 months.

Renal recovery at 90 days is almost essentially the same as recovery at 1 year [20]. Failure to become independent from RRT by 90 days would appear more likely to be associated with progression to end-stage renal disease, and this duration of follow-up for ascertainment of recovery has been recommended by the Acute Dialysis Quality Initiative Group [5].

Renal Recovery from ARF at 5 or More Years

In a large retrospective study, Morgera et al. reported the short- and long-term outcomes in 979 critically ill patients with AKI, presumably secondary due to ATN, treated with continuous RRT. While hospital mortality was 69%, no data were given on renal recovery at hospital discharge. Long-term follow-up was determined by survey of patients, family doctors, or local registries and data on renal prognosis for survivors were available for approximately 50% of patients. Of these 50% patients available for analysis, 40% had evidence of partial recovery, while 10% were RRT-dependent [22].

Korkela et al. described the renal outcome in a small retrospective cohort of critically ill patients with ATN requiring RRT from a single central multidisciplinary intensive care unit. A total of 69 patients (2% of admissions) received RRT. Of these patients 38 (55%) survived to hospital discharge. Long-term survival at 5 years was 35%, and 8% of the initial population needed chronic dialysis [23]

Of an initial population of 413 cases, Liano et al. followed up the cohort of 187 survivors of AKI for 7–22 years (median 7 years). None of the patients had preexisting chronic renal disease; they all had a clinical diagnosis of ATN. The AKI was classified as mild in 20 patients, moderate in 79 patients, and severe in 88 patients. Fifty-seven patients with AKI required dialysis; 80 patients were treated in the ICU; 107 were treated on other hospital wards. Ten patients were lost for follow-up. Renal function at discharge was normal in 78 patients, and mild renal insufficiency was reported in 64 patients; moderate renal insufficiency in 39 patients; and severe renal insufficiency in 6 patients. During the follow-up, three of the 187 survivors of AKI (2%), with severe comorbidity factors required chronic hemodialysis at 6, 11, and 12 years after discharge [24].

Schiffl conducted a prospective 5-year cohort study of 425 patients with severe ATN requiring RRT. None of these patients had renal function impairment as judged by calculated glomerular filtration rate. Of these, 53% of the patients forming the cohort survived the hospital stay. Fifty-seven percent of the survivors of severe ATN leaving the hospital had normal renal function, 33.5% had mild to moderate renal failure (serum creatinine values between 1. 3– 3.0 mg/dl), and 10 had severe renal dysfunction. None of the patients needed RRT at discharge from the hospital. Survival rate at 5-year post discharge was 25 %. Of the 25% long-term survivors, 86% had normal renal function (complete recovery) , 6% had mild renal in-sufficiency, 2% had moderate chronic renal insufficiency , 2% had severe renal failure, and 4% patients had a re-need for dialysis [25].

Survivors with Re-need for Dialysis Therapy

There are a few data on the recurring need for dialysis in survivors form severe AKI. There is no doubt that a proportion of survivors with incomplete recovery at hospital discharge shows deterioration of renal function impairment. Progression to end-stage renal disease clearly depends on the presence of preexisting renal failure, which is the cause of intrinsic renal failure.

However, recurring need for RRT is rarely observed in ICU patients recovering from severe ATN. In our study, 5 out of 106 long-term (5-year) survivors had end-stage renal disease requiring recommencement of dialysis (1% of the initial cohort or 2% of patients discharged from hospital or 5% of long-term survivors). Liano and colleagues reported that 3 out of 177 long-term survivors from ATN required re-institution of dialysis at 6, 11, and 12 years after AKI, respectively [24]. Moreover, Georgaki-Angelaqki et al. measured renal function in children, 7–12 years after recovery from ATN [26].

Conclusion

Renal recovery after acute kidney dysfunction, in particular in critical illness, is an important determinant of long-term heath status, quality of life, and mortality. Nonrecovery or re-need of RRT add a burden to health resources. The available epidemiologic evidence suggests that the majority of patients with severe hospital-acquired AKI achieve independence from RRT. Thus, the old adage that the kidneys recover if patients survive AKI remains true, at least in those with precipitation of ATN on normal kidneys. However, acute kidney dysfunction should no longer be viewed as reversible complication of extra-renal critical illness. Acute Kidney Injury is not only a life-threatening short-term illness, but also an independent determinant of long-term outcome of survivors of AKI.

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