The impact of timing of renal replacement therapy on the outcome of acute kidney injury in critically ill patient: a meta-analysis

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List of Abbreviations

AKI	:	Acute kidney injury
RRT	:	Renal replacement therapy
RCT	:	Randomised controled trials
LOS	:	Length of stay
GFR	:	Glomerular filtration rate
CKD	:	Chronic kidney disease
ESKD	:	End stage kidney disease
RBF	:	Renal blood flow
TGF	:	Tubulo-glomerular feedback
RAAS	:	Renin angiotensin aldosteron system
ATP	:	Adenosine triphosphate
sCR	:	serum creatinine
BUN	:	blood urea nitrogen
NGAL	:	neutrophil gelatinase-associated lipocalin
AKIN	:	AKI Network
KIDGO	:	Kidney Disease Improving Global Outcomes
ADQI	:	acute dialysis quality initiative
QOL	:	Quality of life
CRRT	:	Continuous renal replacement therapies
IHD	:	Intermittent hemodialysis
SLEDD	:	Slow efficiency daily dialysis
EDD	:	extended daily dialysis
CVVH	:	Continuous venovenous hemofiltration
CVVHD	:	continuous venovenous hemodialysis
CVVHDF	:	continuous venovenous hemodiafiltration

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Abstract

Background: Acute kidney injury (AKI) is a common complication in the critically ill patients and associated with a substantial morbidity and mortality. Renal replacement therapy (RRT) remains the primary supportive management strategy for patients with severe AKI. However, the exact timing of initiation of RRT for better patient outcome is still debatable with conflicting data from randomized controlled trials. Thus, a systematic review and meta-analysis was performed to assess the impact of "early" versus "late" initiation of RRT.

Objectives: To investigate the impact of timing of initiation of renal replacement therapy (RRT) on clinical outcomes in critically ill patients with acute kidney injury (AKI), focusing on the randomized controlled trials in this field.

Methods: We enrolled 9 RCTs (since 2000 till 2019) with a total of 1636 patients in this Meta-analysis randomized as early and late groups focusing on mortality up to 90 days, intensive care unit LOS among survivors and non-survivors, hospital LOS among survivors and non-survivors, renal function recovery and renal replacement therapy dependence. The most fundamental differences among the trials were the large differences concerning the timing of RRT initiation among studies. Urine output, serum creatinine, serum urea nitrogen and AKI stages were not used unified in the individual studies to define the early and late RRT strategies.

Results: A pooled analysis of the studies indicated no mortality benefit with "early" RRT, with an RR of 0.97 (95% CI 0.87 to 1.09, P = 0.010). There was no significant difference in intensive care unit (ICU) length of stay (LOS) or hospital LOS between the early and late RRT groups for survivors or non-survivors. Pooled analysis also demonstrated no significant change in renal function recovery (RR 0.99, 95% CI 0.91 to 1.07, I2 = 58.878%), RRT dependence (RR 0.76, 95% CI 0.42 to 1.37, I2 = 0%).

Conclusion: Our meta-analysis revealed that the "early" initiation of RRT in critically ill patients did not result in a reduced Mortality. A pooled analysis of secondary outcomes Showed no significant difference in Intensive care unit Length of stay (LOS) or hospital Length of stay(LOS) between early and late RRT group for survivors or non- survivors.

A pooled analysis also demonstrated no significant change in renal function recovery and RRT dependence.

Key Words: Acute kidney injury, renal replacement therapy, Length of stay

Introduction

Acute kidney injury (AKI) is a common potentially life threatening complication of illnesses among 1% of the community-based population, 8–15% of hospitalized patients, and up to 50% of critically ill patients admitted to the intensive care unit (ICU) ***(Clark et al., 2012).***

AKI carries increased risk of morbidity and mortality and adds to the health- care cost, even in mild temporary form ***(Pannu et al., 2013).***

Although renal replacement therapy (RRT) remains the primary supportive management strategy for patients with severe AKI, it could also be associated with complications and adverse events ***(Schneider et al., 2013).***

Despite improvements in RRT technology, it is still not clear whether the outcome of patients with AKI who require RRT has improved over the years ***(Akhoundi et al., 2015).***

Earlier initiation of RRT may provide a better control of fluid and electrolyte balance, superior acid–base homeostasis, removal of uremic waste, and prevention of subsequent complications attributable to AKI. Furthermore, earlier RRT could potentially limit the kidney-specific and remote organ injuries due to fluid overload, electrolyte imbalance, and systemic inflammation ***(Wald and Bagshaw, 2014).***

However, earlier RRT may also expose the patients to increased risks of hemodynamic instability, anticoagulation induced bleeding, blood stream infection, and even inflammatory or oxidative stress induced by the bio-incompatibility of the dialyzer membranes.

In comparison, later initiation of RRT may allow more time for hemodynamic optimization prior to RRT, and it may avoid the need for RRT and its associated complications ***(Shingarev et al., 2013)***.

In recent decades, the timing of RRT initiation has been evaluated in different population types (e. g., surgical or medical patients). Variability in the definitions of AKI and RRT timing has resulted in contradicting conclusions among the various studies ***(Carl et al., 2010).***

Similarly, previous systematic analyses regarding the optimal timing of RRT initiation were unable to draw definitive conclusions owing to the scarcity of large-scale randomized controlled trials (RCTs), non-standardized triggers for RRT initiation, and heterogeneities of population and study design while the observational studies tended to show more beneficial effects for earlier RRT, clinical trials were unable to replicate these findings ***(Gaudry et al., 2016)***.

Recently, two large RCTs showed contradictory results and attracted considerable attention from both clinicians and researchers. The first was a multicenter RCT

by the AKIKI study group, which showed no significant differences in 60-day mortality between early and delayed RRT groups ***(Gaudry et al., 2016)***.

Another was the ELAIN trial, ***(Zarbock et al., 2016)*** a single-center RCT that showed significant benefits in terms of 90-day mortality, renal function recovery, and hospital length of stay (LOS) among patients in the early RRT group. Although these two RCTs exhibited opposing results, they added value to the field of critical care ***(Zarbock et al., 2016)***.

This systematic review is conducted to include all relevant RCTs related to the impact of the timing of RRT initiation among critically ill patients with moderate to severe AKI.

Aim of the work

To investigate the impact of timing of initiation of renal replacement therapy (RRT) on clinical outcomes in critically ill patients with acute kidney injury (AKI), focusing on the randomized controlled trials in this field.

Review of Literature

DEFINITION

Acute kidney injury is defined as a failure of the kidneys to eliminate waste products and maintain homeostasis of water and electrolytes. However, no definite and measureable parameters have been established for the diagnosis of AKI, and there is no general agreement on what AKI definitely is among clinicians and investigators. In Light of the wide range of definitions available (almost every study published provides a different definition of AKI), it is very difficult to compare experiences and determine the exact incidence and impact of AKI in the critical care setting ***(Han and Bonventre , 2004)***.

When a renal aggression occurs and until the kidneys show any alterations, a compensation mechanism based on decreasing GFR levels is activated ***(Lameire et al., 2005)***.

Yet, such decrease in GFR is not detected early because of the lack of a method that is sensitive enough ***(Seller-Perez et al., 2013)***.

As a result, AKI is only detected in later stages. This problem is worsened by the fact that a standard definition of AKI has not been established yet. A clear framework or ‘‘Standardized Criteria’’ should be established for an objective clinical diagnosis of AKI. These standardized criteria should have sufficient sensitivity and specificity,