Section: Nephrology

Original Research Article

ASSESSMENT OF SHORT-TERM MORTALITY AND RENAL FUNCTION RECOVERY WITH EARLY AND LATE INITIATION OF RENAL REPLACEMENT THERAPY IN AKI PATIENTS

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ABSTRACT

Background: Despite advances in medical diagnosis and treatment the mortality associated with AKI remains high.[3,4,5] Renal replacement therapy (RRT) provides potential treatment to patients with AKI. Nevertheless, it involves complexity of treatment, is associated with higher risk of adverse effects and involves higher costs of treatment in severe AKI patients. Though RRT is key to the management of AKI, but some basic questions about RRT remain unclear. The evidence on early or late initiation of RRT and its impact on mortality outcomes is limited in Indian set up. **Objectives:** To assess short term (28-day) mortality with early and late initiation of RRT in AKI patients and also to assess renal function recovery as defined by KDIGO criteria.
Materials and Methods: This prospective, cross-sectional, observational study was conducted at ICU set up at Yashoda super speciality hospital, Malapet in Hyderabad city during the study period from August 2016 to July 2017.
Results: Majority of patients were above the age group of >60 years (39.8% and 45.4% in two groups respectively). Males predominated in both groups with 70.7% and 65.7% in two groups respectively. Total mortality was significantly lower in the Early RRT group (22.0%) compared to the Late RRT group (38.0%) ($p = 0.008$), indicating a possible survival benefit of initiating RRT early. 28-day mortality showed no significant difference between the two groups (3.0% vs. 2.9%, p = 0.961), suggesting that early initiation mainly impacted overall survival rather than short-term (28-day) outcomes.
Conclusion: Our study finds that 28-day mortality showed no significant difference between the two groups (3.0% vs. 2.9%, p = 0.961), suggesting that early initiation mainly impacted overall survival rather than short-term (28-day) outcomes. We observed that recovery of renal function was also better as none of the patients required RRT at day 28 compared to late strategy.
Keywords: short term mortality, early and late initiation of RRT, AKI, renal function recovery.

INTRODUCTION

Renal injury is a critical medical condition associated with increased morbidity and mortality. Acute kidney injury (AKI) is well recognized illness contributing to increased mortality.[1,2] Despite advances in medical diagnosis and treatment the mortality associated with AKI remains high.[3,4,5] Renal replacement therapy (RRT) provides potential treatment to patients with AKI. Nevertheless, it involves complexity of treatment, is associated with higher risk of adverse effects and involves higher costs of treatment in severe AKI patients. Though RRT is key to the management of AKI, but some basic questions about RRT remain unclear. Increasingly, the optimal timing of RRT initiation is hugely unknown.[6]

Definitions as early and late initiation of RRT have been suggested but are based on arbitrary assumptions. A study assessed impact of timing of RRT initiation on outcomes in post-traumatic AKI patients. Serum blood urea nitrogen was used as a surrogate marker. Significantly improved survival was seen in cases of early than late initiation of RRT (39% Vs 20% respectively, p=0.041).[7] However, in one prospective study using median urea and serum creatinine found no significant difference in outcome (63.4% late and 61.4% early RRT) when stratified by urea but when serum creatinine was used as marker, late RRT was beneficial (53.4% Vs 71.4%, p<0.0001).[8] A study dividing patients in early and late by RIFLE criteria reported high mortality in late RRT group (74.5% Vs 43.1%, p=0.002).[9]

The evidence on early or late initiation of RRT and its impact on mortality outcomes is limited in Indian set up. Therefore, we planned this prospective study to assess effect of early RRT or late RRT initiation on outcomes in patients.

Objectives: To assess short term (28-day) mortality with early and late initiation of RRT in AKI patients and also to assess renal function recovery as defined by KDIGO criteria.

MATERIALS AND METHODS

This study was conducted at Yashoda super speciality hospital, Malapet in Hyderabad city. Methodology adopted for this study is discussed below.

Study Design: This study was a prospective, cross-sectional, observational study.

Research Setting: The study was conducted at ICU of a tertiary care teaching hospital which caters to urban as well as rural population in central parts of India. The site was medicine outpatient and inpatient department of this hospital.

Duration of Study: Study was carried out in August 2016 and was be completed in July 2017. Total duration was for 12 months.

Ethical Approval: Institutional ethics committee approval of the protocol of the study was taken. Only after ethical approval, patient recruitment in to the study was started.

Study population: This study was done in patients under settings of medicine department. All patients who were diagnosed newly with acute kidney injury (AKI) were eligible to enter the study.

The criteria to define AKI based on serum creatinine and urine output is shown in table 1.

Table 1: Classification of AKI by KDIGO Guideline

Stage	Serum Creatinine (SCr)	Urine Output
1	Increase of 0.3 mg/dL or more or increase of 1.5 to1.9 times from baseline.	<0.5 mL/kg/h for more than 6 to 12 hours
2	Increase of more than 2 to 2.9 times from baseline	<0.5 mL/kg/h for more than 12 hours
3	Increase of more than 3 times from baseline (>3-fold) or levels of 4.0 mg/dL or initiation RRT	<0.3 mL/kg/h for 24 hours or Anuria for 12 hours

After signing an informed consent form, these patients were screened with following inclusion and exclusion criteria for recruiting in to the study.

Inclusion Criteria

- Diagnosed as AKI due to non-renal causes
- Age ≥ 18 yrs
- Both gender
- Patients were willing to give informed written consent

Exclusion Criteria

- Preexisting chronic kidney disease
- Previous RRT
- AKI due to following reasons
  - permanent occlusion or surgical lesion of the renal artery
  - glomerulonephritis, interstitial nephritis or vasculitis
  - Prior kidney transplantation
  - Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura
- Pregnancy
- Hepato-renal syndrome

Treatment Arms:

Early RRT: Initiation of RRT at stage 2 of the KDIGO classification within 8 hours

- Urine output <0.5 ml/kg/h for ≥12 h; and/or
  - Two-fold increase of the serum creatinine level compared to the baseline value.

Late RRT: Initiation of RRT when stage 3 of the KDIGO classification (not later than 12 hours after achieving stage 3) is achieved:

- Urine output <0.3 ml/kg/h for ≥24 h; and/or
- More than three-fold increase of the serum creatinine level compared to the baseline value; and/or
- Serum creatinine of ≥4 mg/dl with an acute increase of at least 0.5 mg/dl within 48 hours.

RRT was also be considered for any of the following ABSOLUTE indications

- Urea serum levels >100 mg/dl;
- Potassium serum levels >6 mmol/l and/or ECG abnormalities;
- Magnesium serum levels >4 mmol/l;
- Urine production <200 ml/12 h or anuria (without diuretics, according to the KDIGO recommendations); and
- Organ edema in the presence of AKI resistant to diuretic treatment (one attempt with loop diuretics prior to randomization).

Patient management:

After enrolment, investigators performed catheter insertion and initiate RRT. Patients were under constant care of nephrologist during the RRT duration. Investigator nephrologist was performed daily visits to ensure adherence to the protocol.

Hemodynamic, renal and laboratory data was be documented.

All patients enrolled in to the study were receive standard intensive care therapy. As there is no proven pharmacological therapy for AKI, the management of AKI remains primarily supportive, with renal replacement therapy serving as a cornerstone of therapy for patients with severe kidney injury. None of the patients in both groups ('early' and 'late' groups) were exposed to any other additional risks.

Outcome Assessments

The primary endpoint in this study is overall survival in a 28-day follow-up period.

Secondary outcomes include:

- Overall survival in a 14-day follow-up period
- Recovery of renal function as defined in the KDIGO guidelines
- Requirement of haemodialysis after day 14 and day 21;
- Duration of renal support;
- ICU and hospital length of stay

Data Collection

Data collection was performed pseudonymously and the patient's name were not appeared on any case report form (CRF). All data was kept confidential. The treating investigator was informed the patient about the nature of the trial, its aims, expected advantages as well as possible risks. Written informed consent was obtained from eligible patients and in case of patient incapacity by the legally authorized representative.

Sample Size; minimum 100 cases were taken.

Statistical Analysis Plan

Descriptive analyses was performed on all baseline variables including means and standard deviations, medians and quartiles (quartile 1 [Q1], quartile 3 [Q3]), or frequency and percentages, as appropriate. Binary data was tested for significance using the $\chi 2$ test or Fisher exact test where appropriate. Event rate was compared by calculating the odds ratio [OR] and absolute risk reduction with associated asymptotic 95% confidence intervals. Normally distributed data was tested for significance using t tests. For non-normal data the Mann-Whitney U test was applied.

RESULTS

Table 1: Age distribution in study population

Age	Early RRT (n=123)	Late RRT (n=108)	P value
≤30	2 (1.6)	12 (11.1)	0.013
31-40	14 (11.4)	9 (8.3)	
41-50	21 (17.1)	18 (16.7)	
51-60	37 (30.1)	20 (18.5)	
>60	49 (39.8)	49 (45.4)	
Mean ± SD	55.6±11.7	55.7±15.9	0.945

Mean age of the patients did not differ in two groups. Majority of patients were above the age group of >60 years (39.8% and 45.4% in two groups respectively).

Table 2: Gender distribution

Gender	Early RRT (n=123)	Late RRT (n=108)	P value
Female	36 (29.3)	37 (34.3)	0.416
Male	87 (70.7)	71 (65.7)	

Males predominated in both groups with 70.7% and 65.7% in two groups respectively.

Table 3: Mortality outcome

Mortality	Early RRT	Late RRT	P value
Total	27 (22.0)	41 (38.0)	0.008
Day 28	3 (3.0)	2 (2.9)	0.961

Total mortality was significantly lower in the Early RRT group (22.0%) compared to the Late RRT group (38.0%) ($p = 0.008$), indicating a possible survival benefit of initiating RRT early. 28-day mortality showed no significant difference between the two groups (3.0% vs. 2.9%, $p = 0.961$), suggesting that early initiation mainly impacted overall survival rather than short-term (28-day) outcomes.

Table 4: Renal function recovery

Renal function recovery	Early RRT (n=99)	Late RRT (n=69)	P value
Yes	83 (83.8)	55 (79.7)	0.492
No	16 (16.2)	14 (20.3)	

From among the survivors, most patients recovered renal function by day 28 (83.8% and 79.7% p=0.492).

DISCUSSION

Mean age of population in early and late RRT group was 55.6±11.7 and 55.7±15.9 years respectively and there was no significant difference in age (p=0.945). In different age groups, there was increasing proportion of patients from younger age group to older age group showing maximum number of patients in age group of >60 years (39.8% and 45.4% in two groups respectively). This difference in proportion of different age groups was significant (p=0.013). In a similarly conducted ELAIN-Trial from Zarbock et al10 mean age of the patients in two groups was 65.7±13.5 and 68.2±12.7 years respectively. Study from Bagshaw et al,[11] reported age of 59.9±19.9 year in early RRT group and 63.3±14.9 years in late RRT group and difference was statistically significant (p=0.0002).

Males predominated in our study with 70.7% and 65.7% in early and late RRT group respectively. Zarbock et al,[10] also observed higher proportion of males with 69.6% and 57.1% in two groups. Bagshaw et al,[11] also found similar results with 61.9% and 67.3% males in early and late RRT group.[11]

28-day mortality showed no significant difference between the two groups (3.0% vs. 2.9%, p = 0.961), suggesting that early initiation mainly impacted overall survival rather than short-term (28-day) outcomes.

The 28-day mortality in study from Zarbock et al,[10] was 30.4% and 40.3% (p=0.11) in two groups finding no significant difference. However, day 90 mortality was significantly less in early RRT group (39.3% vs 54.7%, p=0.03).[12]

Liu et al,[12] also reported slightly lower crude survival rate for late RRT. They reported survival at day 14 and 28 of 0.80 and 0.65 (i.e. mortality rate of 20% and 35%) for early RRT against 0.75 and 0.59 (i.e. mortality rate of 25% and 41%) for late RRT.

From early and late RRT groups, 16.2% and 20.3% patients did not recover the renal function at day 28. Zarbock et al,[10] reported nearly similar figures with 11.8% and 14.8% patients from early and late RRT group having not recovered renal function at day 90. Gaudry et al,[13] reported that 12% and 10% patients from two groups respectively were still dependent on RRT at day 28 suggesting these patients had probably not recovered the renal function.

CONCLUSION

Our study finds that 28-day mortality showed no significant difference between the two groups (3.0% vs. 2.9%, p = 0.961), suggesting that early initiation mainly impacted overall survival rather than short-term (28-day) outcomes. We observed that recovery of renal function was also better as none of the patients required RRT at day 28 compared to late strategy.

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