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Comparison of early continuous hemodiafiltration vs. delayed continuous hemodiafiltration in patients of acute kidney injury (AKI) with septic shock

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Abstract

Introduction: Acute kidney injury (AKI) is a common clinical condition among critically ill patients, incredibly complicated with sepsis. The study aims to compare mortality rates in early and late renal replacement therapy initiation in critically ill patients with AKI and septic shock.

Methods and Material: We carried out a retrospective, randomized, single-centre study of early vs. late RRT-implementation strategies for critically ill patients with sepsis and AKI in ICU at our Institute for one year (July 2017 to July 2018). AKI was defined and categorized by RIFLE criteria.

Results: A total of 59 deaths were observed by day 28 (25 in the early RRT group and 34 in the delayed RRT group). The survival rates were estimated using the Kaplan–Meier method and compared with a log-rank test (p=0.007). The Kaplan–Meier estimate of the overall survival at day 28 was 49.1% (95% CI, 45.0 to 52.9).

Conclusions: Among critically ill patients with sepsis with AKI, we observed reduced 28-day mortality in early RRT than delayed RRT initiation. Our study proves the benefit of early implementation of CRRT over delayed therapy with better 28-day survival in the early RRT group.

Keywords: Acute Kidney Injury; Renal replacement therapy; Septic Shock

1. Introduction

Acute kidney injury (AKI), a common clinical condition among critically ill patients, mainly with sepsis[1]. The abrupt deterioration of renal function characterizes it due to the retention of endogenous or exogenous toxic metabolites. This further depletes glomerular filtration rate (GFR), an increase in serum creatinine and fluid, electrolyte, and water imbalance.

Renal replacement therapy (RRT) is highly beneficial in AKI as it rapidly reverses complications associated with AKI, such as metabolic acidosis, hyperkalemia, or fluid overload. However, the timing of initiation is highly debated and controversial. Early initiation of renal replacement therapy (RRT) is beneficial in avoiding complications due to AKI by preventing hypervolemia, eliminating toxins, initiating acid-base homeostasis, and any other difficulty[2]. It is also beneficial in preventing irreversible organ injury from toxic hyperkalemia and refractory metabolic acidosis. It also provides adequate time for kidneys to recover from damage[3]. It is hypothesised that preventing irreversible organ damage may lead to better survival and reduced hospital length of stay. On the other hand, early initiation of RRT may

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cause unnecessary exposure to potential harm because some patients will spontaneously recover renal function. However, insufficient evidence exists to determine the optimal timing of initiation of RRT[3].

We planned this randomised, retrospective single-centre study intending to compare mortality rates in early and delayed initiation of RRT in critically ill patients with AKI and sepsis.

2. Material and methods

2.1. Sample collection

In this retrospective randomized single-centre study in a mixed surgical ICU, we analysed 84 critically ill patients with sepsis for one year (July 2017 to July 2018). The study was approved by Royal Pune Independent Ethical Committee and study was conducted as per the World Medical Association Declaration of Helsinki. The data of all adult patients between 18- 90 years of age requiring admission in ICU.

Of these 84 patients, 42 had received early RRT (Risk, injury, failure, loss of kidney function, and end-stage kidney disease; RIFLE-I) and 42 received delayed RRT (RIFLE-F). The characteristics of the patients were well balanced between the two groups. The early-strategy group patients underwent CRRT when in RIFLE Injury, while all those in the delayed group received renal replacement therapy when they reached stage RIFLE Failure. We excluded patients with any pre-existing renal disease, previous renal replacement, transplant, pregnancy, AIDS, and malignancy from the study.

2.2. Power and sample size

Power calculations are performed based on the primary endpoint, i.e., the overall survival in a 28-day follow-up period. We applied a global (2-sided) significance level α of .05. The expected 28- day survival rate in the control group with delayed RRT initiation was 29% based on the literature, with a power of 80%. The expected treatment effect of 18% was calculated on the mortality differences between early and delayed RRT reported in prior studies[11]. The required sample size for the final analysis was 40 patients per treatment group, 80 patients in total. We used a block randomization technique.

2.3. Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of the data. We presented continuous variables as Mean ± SD and Categorical variables as numbers & percentages. Overall survival (OS) was calculated using the Kaplan-Meier method & the log-rank test assessed the differences in subgroups. We calculated proportional hazards models and hazard ratios (HRs) with associated 95% confidence intervals. Multivariable statistical analysis of the primary outcome was performed using Cox regression. A Chi-square test was done to compare qualitative data. All P-values were two-sided, and $p < 0.05$ was considered significant. We used the SPSS (Statistical Package for Social Sciences) Version 15.0 software for statistical analysis.

3. Results

We observed a total of 59 deaths by day 28 (25 in the early-strategy group and 34 in the delayed-strategy group). The survival rates were estimated using the Kaplan–Meier method and compared with a log-rank test (P = 0.007). The Kaplan–Meier estimate of the overall survival at day 28 was 49.1% (95% confidence interval [CI], 45.0 to 52.9). Early initiation of RRT significantly improved 28-day survival compared with delayed initiation of RRT, 17 of 42 patients [40.4%] in the early group v/s 8 of 42 patients [19.0%] in the delayed group; *P = 0.001*; Hazards Ratio, 0.41 [95% CI, 0.24 to 0.70]. The hazard ratio probability of dying shows that the early treatment group has a probability of 0.2 times of death than the delayed treatment group that is survival is five times better in the early treatment group. Kaplan Meier curve for survival probability. The results are as shown in Figure-1.

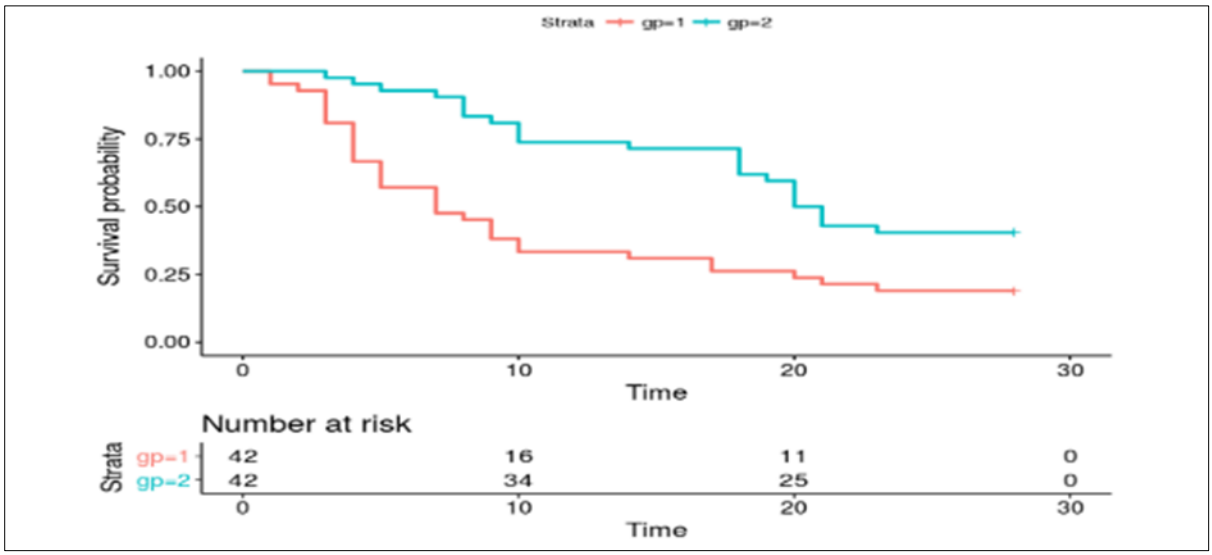

Figure 1 Kaplan Meier curve of survival probability

After taking all co-factors (serum creatinine, serum urea, serum potassium, bicarbonate, lactate, and pH) into account, even then the early treatment group's survival is more than the delayed treatment group ($p = 0.009$) as calculated by the Cox proportional hazards test. However, survival benefit has not been seen when age and sex have been factored in with the other co-factors. The change in blood urea before and after initiation of CRRT was found to be statistically significant between the early and delayed group ($p < 0.05$). The Welch two-sample t-test evaluated change in serum creatinine (before and after CRRT), compared between the early and delayed treatment groups, and the difference was found to be statistically significant ($p < 0.001$). However, the mean and standard deviations for changes in serum creatinine, serum urea, serum potassium, lactate, and pH were found to be lower in the early group. However, this did not translate to survival benefits, as described earlier. The change in bicarbonate before and after initiation of CRRT was found to be statistically significant between the early and delayed group ($P < 0.001$). Among all laboratory parameters, bicarbonate was also a statistically significant independent predictor of better survival ($P < 0.05$). The change in lactate before and after initiation of CRRT was found to be statistically significant between the early and delayed group ($P < 0.001$).

4. Discussion

Critically ill patients with AKI have poorer prognosis as they frequently develop infections and malignancies. These patients often have very high inflammatory mediators (IL-6, IL-8, IL-18), which often contribute to increased mortality[3]. A hypothesis states that early initiation of RRT reduces plasma levels of these inflammatory mediators. On the other hand, it increases the cost and may unnecessarily expose patients to RRT. Therefore, the optimal timing of initiation of renal replacement has been a topic of debate. Instead, it has been given a high priority in research by Acute Kidney Injury Network (AKIN)[4,5]. Our study compared early RRT with delayed therapy concerning improved survival and laboratory parameters.

A meta-analysis suggests that earlier initiation of RRT in critically ill patients with AKI may benefit survival[2]. The data from various studies have been contradicting. Karvellas et al[6]. performed a meta-analysis and systematic review comparing early with the late initiation of renal replacement to treat ICU patients with AKI collecting information from 15 studies in their meta-analysis. They observed reduced mortality (OR= 0.45, 95 % CI = 0.26- 0.72), reduced RRT duration, and a significant reduction in hospital length of stay. However, since there was a lot of heterogeneity in the study population and the overall quality of study design methodology was low, they could not make a definitive recommendation based on the meta-analysis. In another meta-analysis study by Pasin L et al.[7], there was no clinically relevant advantage in the early initiation of RRT in critically ill patients with AKI than those with late RRT. In a retrospective single-center study on 60 Korean patients with AKI-SA, they evaluated the effect of early and delayed initiation of RRT on mortality in a 28-day study period. The results suggest a significantly higher 28-day mortality in the late CRRT group than that of the early CRRT group (30% vs. 56.7%)[8]. Various other researchers reported similar results[9,10]. Like the above-stated studies, our retrospective study also suggests a significant improvement in the 28-day mortality in the early RRT group compared to that of the delayed RRT group (40.4% vs. 19%, $p = 0.001$). In ELAIN randomised clinical trial[11], consisting of 231 patients, they observed a dramatic reduction in 90-day mortality in the

early RRT group (39.3%) compared to 53.7% in the delayed RRT group. In a similar randomised trial by Bouman et al.[12], on 106 AKI patients, there was no difference in survival in terms of timing of initiation of RRT or varying ultrafiltration rates (Blood flow rate 200ml/min in high flow group v/s 100 ml/min in low flow group). However, they opined that high filtration techniques might be advantageous in logistic reasons- dialysis sessions could be interrupted. The machine could be shared with other patients, and it may help mobilise patients. In a recent review article by Agapito Fonseca J et al[13], a compilation of various small, retrospective, non-double blinded studies demonstrate contradictory results pertaining the benefits of initiation of early RRT in AKI patients. The definition of early and late RRT needs to be further standardized and optimal time of treatment time needs to be defined.

A small randomized clinical trial demonstrated that RRT's early initiation was associated with reduced mortality compared with RRT's late initiation[14]. In this study, the authors evaluated early RRT's role in 28 patients with AKI following cardiac surgery. Fourteen patients were started on continuous haemodialysis when their urine volume decreased to less than 30mL/h for 3 hours. In patients in the "late" group (n = 14), RRT was delayed until urine output had fallen to less than 20 mL/h for 2 hours. Survival was significantly better in the group of patients who started RRT earlier. Based on the available literature, the optimal timing of initiation of CRRT is still confusing.

As reported and stated by the RIFLE, AKIN of KIDGO classification, the initiation of early RRT in AKI group may help in retaining the acid-base and electrolyte equilibrium, prevent hypervolemia which otherwise can be deleterious and increase the mortality rate[15]. The same has been reported in various studies[16, 17]. Most studies associate the elevated levels of serum creatinine and urea, lower urinary output as indications of delayed initiation of RRT[15]. In our study we considered various cofactor evaluation to understand their role in early and delayed RRT and the results depict better survival in the early treatment group over the 28-day period ($P = 0.009$) and also a significant change in the serum creatinine value before and after the initiation of treatment ($P < 0.001$).

Our study did not reveal statistical difference between the early and late RRT group concerning mortality (38% vs 41.4 %).

Potential benefits of earlier initiation are attributable to more rapid metabolic or uremic control and more effective prevention and management of fluid overload. Some data suggest that RRT before the onset of severe AKI may attenuate kidney-specific and non–kidney organ injury from academia, uremia, fluid overload, and systemic inflammation and could potentially translate into improved survival and earlier recovery of kidney function. The counterargument: early RRT might subject patients who would recover renal function with conservative treatment to RRT's potential risks. However, AKI confers a substantially increased risk of death even in patients never treated with RRT. As such, although there may be a risk of "unnecessary" RRT, there could be an even greater risk associated with not providing it.

5. Conclusion

Among critically ill patients with sepsis with AKI, early RRT compared with RRT's delayed initiation reduced mortality over the first 28 days. Although we detected a massive mortality difference in our study group, this was not a multicentre trial. Hence, our results may inflate the observed effect size. Therefore, more randomized multicentre trials are required to answer this question.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

If studies involve use of animal/human subject, authors must give appropriate statement of ethical approval. If not applicable then mention 'The present research work does not contain any studies performed on animals/humans subjects by any of the authors'.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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