AJKD
Original Investigation

Earlier-Start Versus Usual-Start Dialysis in Patients With Community-Acquired Acute Kidney Injury: A Randomized Controlled Trial

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Background: Optimum timing of the initiation of dialysis therapy in acute kidney injury is not clear.

Study Design: Prospective, open label, 2-arm, randomized, controlled trial.

Setting & Participants: 208 adults with acute kidney injury with progressively worsening azotemia at the artificial kidney dialysis unit of a tertiary-care referral center in western India.

Intervention: Earlier-start dialysis was initiated when serum urea nitrogen and/or creatinine levels increased to 70 and 7 mg/dL, respectively, whereas the usual-start dialysis patients (control group) received dialysis when clinically indicated as judged by treating nephrologists.

Outcomes: Primary outcome was in-hospital mortality and dialysis dependence at 3 months. Secondary outcome in patients receiving dialysis was time to recovery of kidney function, computed from time of enrollment to the last dialysis session.

Results: Of 585 screened patients, 102 were assigned to earlier-start dialysis, and 106 to usual-start dialysis. Baseline characteristics were similar between randomized groups. 93 (91.1%) and 88 (83.1%) participants received dialysis in the intervention and control groups, respectively. Mean serum urea nitrogen and serum creatinine levels at dialysis therapy initiation were 71.7 ± 21.7 (SD) and 7.4 ± 5.3 mg/dL, respectively, in the intervention group versus 100.9 ± 32.6 and 10.41 ± 3.3 mg/dL in the control group. Data on primary outcome were available for all patients. In-hospital mortality was 20.5% and 12.2% in the intervention and control groups, respectively (relative risk, 1.67; 95% CI, 0.88-3.17; $P = 0.2$). 4.9% and 4.7% of patients in the intervention and control groups, respectively, were dialysis dependent at 3 months (relative risk, 1.04; 95% CI, 0.29-3.7; $P = 0.9$).

Limitations: Study was not double blind, event rate (ie, mortality) was less than predicted, wide CIs preclude definitive findings.

Conclusions: Our data do not support the earlier initiation of dialysis therapy in community-acquired acute kidney injury.

Am J Kidney Dis. 62(6):1116-1121.

INDEX WORDS: Acute kidney injury; dialysis start; mortality; dialysis dependence.

Editorial, p. 1030

Acute kidney injury (AKI) is present in 5% of hospitalized patients and is associated with high mortality (range, 20%-60%).[1-3] More than 200 years after AKI was first described as "ischuria renalis" by William Heberden,[4] therapy to alter the natural course of tubular injury remains elusive and treatment is mainly supportive. Dialysis is required in some of these patients to treat various complications of AKI before kidneys recover. Data for the optimum time to start dialysis therapy are lacking and are considered as one of the top research priorities in AKI.[5,6] Systematic reviews and meta-analyses addressing this issue have concluded that available data are inconclusive and have suggested the need for a randomized controlled trial on the correct timing of dialysis therapy initiation.[5,7,8]

Available research on the treatment of AKI is related principally to critically ill patients in intensive care unit settings. Community-acquired AKI is the most common renal emergency in developing countries and contributes to one-third of the global AKI burden.[9] In contrast to sepsis-associated AKI in the critically ill, community-acquired AKI is characterized by younger age of the affected population, less severe extrarenal organ dysfunction, lower comorbid condition burden, and an overall better outcome.[9,10]

In the absence of data from prospective trials, practice regarding the initiation of dialysis therapy in AKI varies widely and dialysis before the onset of overt complications of kidney failure often is used. Whether earlier initiation of dialysis therapy improves survival in AKI is not known. A single prospective randomized

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Received February 15, 2013. Accepted in revised form June 10, 2013. Originally published online August 12, 2013.

Trial registration: www.ctri.nic.in; study number: CTRI/2011/12/002255.

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0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2013.06.012

trial to evaluate the impact of timing of initiation on outcome concluded that early dialysis does not improve survival.[10] However data from an observational study and other smaller studies supported the strategy of earlier initiation of dialysis therapy.[11-14]

We conducted a randomized controlled trial to test the hypothesis that earlier-start dialysis therapy would reduce mortality in patients with AKI.

METHODS

Trial Design

This was a single-center, prospective, randomized, parallel-group trial of the 2 strategies of initiation of dialysis therapy in AKI conducted from April 3, 2011, to July 28, 2012, at the department of nephrology of a tertiary-care teaching hospital in western India.

Adult patients of either sex with AKI referred for nephrology consultation were screened for study entry. Participants were eligible for randomization if they had severe AKI with increasing serum urea nitrogen and creatinine levels. Patients who required urgent dialysis for life-threatening uremic complications (ie, treatment-refractory hyperkalemia and fluid overload, alteration of higher mental function attributable to uremia, and pericarditis), who received dialysis therapy before evaluation, and who were judged to be in the recovery phase were excluded. Written informed consent was obtained from patients or their health care surrogates before participation. The study protocol was approved by an institutional ethics committee, CARE (Committee for Academic Research Ethics).

Sample Size

Based on data from previously reported AKI cohorts (from the BEST[1] Kidney [Beginning and Ending Supportive Therapy for the Kidney] and PICARD[3] [Program to Improve Care in Acute Renal Disease] work groups), we assumed the baseline mortality of AKI to be 40% and estimated that a sample size of 80 per treatment arm would be required to detect a reduction to 20% mortality in the 2 treatment arms with 80% power and $\alpha = 0.05$. To account for recovery without dialysis and loss to follow-up, final sample size per arm was decided as 100.

Randomization

Computer-generated block randomization was created by a research fellow not involved in the trial, with block sizes of 52, 42, 54, and 62. Sealed opaque envelopes containing treatment assignment were prepared and the name of the eligible participant was written on it after eligibility screening. Authors M.K., K.J.P., V.K., S.J., and D.M. screened participants and informed authors T.E.J. and N.K.H. when inclusion criteria were met; these 2 authors then confirmed eligibility for study entry. T.E.J. opened the envelope and directed further treatment. Blinding was not possible; however, the study team was not aware of aggregate outcomes during the study.

Study Treatments

Participants were monitored closely for vital parameters, volume status, and clinical and laboratory evidence of uremic complications. They were evaluated by a renal dietitian for nutrient intake and necessary interventions. Nephrologists evaluated patients daily, with their assessment focusing on fluid balance, complications of uremia, and the decision to initiate dialysis therapy or continue expectant management. Physicians and trained nurses monitored participants 24 hours per day.

Patients in the earlier-start dialysis arm (intervention group) had initiation of dialysis therapy if serum urea nitrogen level increased to >70 mg/dL and/or creatinine level increased to >7 mg/dL irrespective of complications. Patients in the usual-start dialysis arm (control group) were treated conservatively with fluid and salt restriction as per urine output, bicarbonate therapy to correct acidosis, and antihyperkalemia therapy and diuretics as clinically indicated, which was decided by consensus of 2 nephrologists. Patients were assessed by a renal dietitian at baseline and then periodically to maintain adequate calorie and protein intake within the limits of recommended daily fluid allowance. Dialysis therapy was initiated only if participants developed complications such as treatment-refractory hyperkalemia, volume overload, and acidosis. Uremic nausea and anorexia leading to inability to maintain nutrient intake also were indications to initiate dialysis therapy.

Intermittent hemodialysis was used as the dialysis modality in most study participants. Hemodialysis was performed by double-lumen noncuffed catheter with blood flow of 200-300 mL/min and dialysate flow of 500 mL/min, with lower blood and dialysate flow in hemodynamically unstable patients. A hollow-fiber polysulfone low-flux dialyzer membrane was used for hemodialysis. Once initiated, intermittent hemodialysis was continued every alternate day (except Sunday) until recovery, with each session lasting 4 hours. A bicarbonate bath was used for dialysis and heparin was used as an anticoagulant unless contraindicated due to coagulopathy. If absolutely indicated, dialysis therapy could be initiated at any degree of azotemia in both treatment arms. All participants were followed up until any of the following 3 outcomes: recovery of kidney function, death, or dialysis dependence (judged at the end of 3 months).

Outcomes

Onset of recovery was judged by a progressive increase in urine output associated with a decrease in serum urea nitrogen and creatinine levels, leading to successful discontinuation of dialysis therapy. The primary end point of the study was in-hospital mortality and dialysis dependence at the end of 3 months. Secondary end points were time to renal recovery in days and, to avoid censoring by death, renal failure−free days. Time to recovery was computed from the time of enrollment to the last dialysis session needed. Data for bleeding complications, number of catheter-related complications including infections, number of episodes of intradialysis hypotension, and requirement of blood product transfusions also were collected.

Statistical Methods

Primary outcomes were analyzed by χ^2 test and are presented as risk ratio. The secondary outcome, in other words, time to recovery, was compared by t test. To account for censoring by mortality, renal failure−free days also were compared using Mann Whitney test. Kaplan-Meier survival curves were plotted for the intervention and control groups. Analysis was by intention to treat. Participants who recovered without dialysis in either group were included in the analysis in the originally assigned treatment arms.

RESULTS

From April 2011 to June 2012, a total of 585 patients with AKI referred for nephrology consultation were screened for study entry (Fig 1). Of 208 eligible patients, 102 were randomly assigned to the earlier-start arm (intervention), and 106, to the usual-start dialysis (control) arm. Outcome data for all study

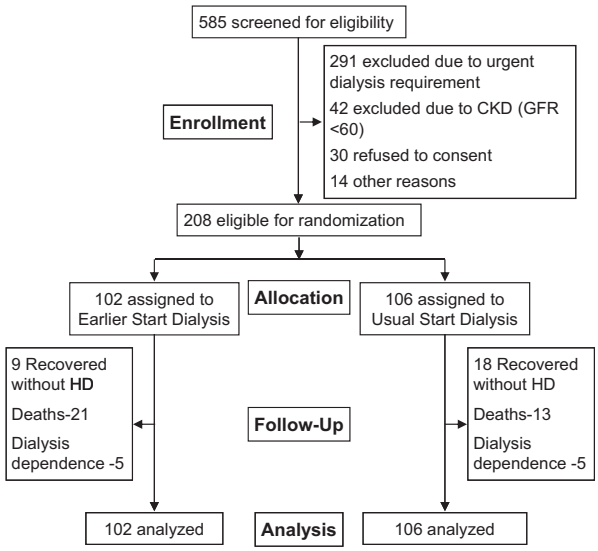

Figure 1. Study flow chart. Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; HD, hemodialysis.

participants were available and there were no losses to follow-up.

Baseline characteristics of the 2 arms were similar, including mean age, comorbid conditions, blood pressure at presentation, Sequential Organ Failure Assessment (SOFA) score, and urine output at presentation (Table 1). Tropical infections (such as malaria, leptospirosis, dengue, hepatitis, and gastroenteritis) and obstetric causes contributed to 53.4% of total cases, whereas sepsis-associated AKI was seen in 26.0% of cases. Mean age of the study population was 42.4 ± 15 (SD) years and 56.3% of the study population did not have significant comorbid conditions before the onset of AKI. At study entry, 73.6% of patients were oliguric. More male participants were allocated to the control arm.

Mean serum creatinine levels at the initiation of dialysis therapy were 7.43 and 10.59 mg/dL in the intervention and control groups, respectively. Mean serum urea nitrogen levels at dialysis therapy initiation were 71.7 and 100.9 mg/dL in the earlier-start and usual-start groups, respectively (Table 2).

Eighteen (17.0%) patients in the control group and 9 (8.8%) in the intervention group recovered without dialysis. This subgroup of the study was characterized by younger age (40 vs 42 years; $P = 0.4$), less severe extrarenal organ dysfunction (SOFA score, 7.6 vs 8.0; $P = 0.6$), and higher urine output at presentation (665 vs 359 mL/d; $P < 0.001$).

Fifteen (14.0%) participants in the control group needed dialysis therapy initiation at a serum creatinine level <7 mg/dL, and 10 (9.8%) in the intervention group required initiation of dialysis therapy before the prespecified level of azotemia. All these participants were included for analysis in the originally assigned treatment arm as per intention-to-treat analysis.

Table 1. Baseline Characteristics

	Earlier-Start Dialysis (n = 102)	Usual-Start Dialysis (n = 106)	P
Age (y)	42.8 ± 15	42.1 ± 15.7	0.7
Male sex	62 (60.8)	79 (74.5)	0.04
Comorbid conditions			
Diabetes mellitus	9 (8.8)	14 (13.2)	0.4
Hypertension	15 (14.7)	24 (22.6)	0.2
Pulmonary tuberculosis	12 (11.7)	6 (5.6)	0.2
HIV infection	4 (3.9)	5 (4.7)	0.9
Coronary artery disease	—	2 (1.8)	
Cause of AKI			
Sepsis	20 (19.6)	24 (22.6)	0.7
Acute gastroenteritis	15 (14.7)	16 (15.0)	
Malaria	11 (10.7)	9 (8.4)	
Undifferentiated acute febrile illness	8 (7.8)	13 (12.2)	
Leptospirosis	3 (2.9)	3 (2.8)	
Dengue	2 (1.9)	3 (2.8)	
Acute hepatitis	3 (2.9)	3 (2.8)	
Obstetric	8 (7.8)	4 (3.7)	
Drug induced	10 (9.8)	9 (8.4)	
Acute pancreatitis	3 (2.9)	4 (3.7)	
Pigment induced	2 (1.9)	2 (1.8)	
Postsurgery	3 (2.9)	—	
Snake bite	3 (2.9)	—	
Tumor lysis	3 (2.9)	—	
Toxic	1 (0.9)	—	
Other	7 (6.8)	5 (4.7)	
Shock at admission	28 (27.4)	24 (22.6)	0.5
SOFA score at admission	7.6 ± 3.3	8.2 ± 3.1	0.2
SOFA score at 48 h	7.2 ± 3	7.7 ± 2.9	0.2
Oliguria	75 (73.5)	78 (73.5)	0.8
Urine output at presentation (mL/d)	429 ± 388	376 ± 350	0.3
≥1 extrarenal organ dysfunction	78 (76.4)	89 (83.9)	0.2

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation.

Abbreviations: AKI, acute kidney injury; HIV, human immunodeficiency virus; SOFA, Sequential Organ Failure Assessment.

Twenty-one of 102 (20.6%) patients in the intervention group died compared with 13 of 106 (12.3%) in the control group (relative risk [RR], 1.67; 95% confidence interval [CI], 0.88-3.17; $P = 0.2$; Fig 2; Table 3). Five patients in each treatment arm were dialysis dependent at 3 months (RR, 1.04; 95% CI, 0.29-3.7; $P = 0.9$; Table 3). Time to recovery of kidney function in patients undergoing dialysis was significantly longer in the intervention group compared to the control group. The number of intradialysis hypotension episodes, bleeding complications, requirement of blood transfusions, and catheter-related bacteremia episodes were similar between the 2 groups.

Table 2. Dialysis Parameters

	Earlier-Start Dialysis	Usual-Start Dialysis	Difference[a] (95% CI)	*P*
SUN at dialysis initiation (mg/dL)	71.7 ± 21.7	100.9 ± 32.6	+29.2 (21.8 to 36.8)	0.01
Creatinine at dialysis initiation (mg/dL)	7.4 ± 5.3	10.4 ± 3.3	+3.0 (1.8 to 4.2)	<0.001
Duration of dialysis support (d)	7.13 ± 8.58	5.30 ± 4.58	−1.8 (−3.71 to 0.05)	0.06
Recovered without dialysis	9 (8.4)	18 (16.9)	+0.08 (−0.008 to 0.17)	0.1
Indication for dialysis				
Protocol earlier start	85 (83.3)	—		
Uremic symptoms	3 (2.9)	61 (57.5)	+0.55 (0.44 to 0.64)	<0.001
Metabolic acidosis	3 (2.9)	—		
Need for transfusions	2 (1.9)	4 (3.7)	+0.01 (−0.03 to 0.07)	0.7
Hyperkalemia	1 (0.9)	7 (6.6)	+0.05 (0.002 to 0.12)	0.001
Volume overload	1 (0.9)	14 (13.2)	+0.12 (0.05 to 0.2)	0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation.

Abbreviations: CI, confidence interval; SUN, serum urea nitrogen.

[a]Mean or proportion difference; usual-start value less earlier-start value.

DISCUSSION

In this prospective randomized trial, we showed that earlier start of dialysis therapy before the onset of significant hyperkalemia, hypervolemia, or uremia does not improve survival and delays the recovery of kidney function in patients with community-acquired AKI. Our results support the findings of the only randomized trial addressing this issue (from Bouman et al[15]). In that study of 106 patients, the authors randomly assigned cases to early high-volume continuous venovenous hemofiltration (CVVH), early low-volume CVVH, and late low-volume CVVH. At 28 days, survival was equivalent in all 3 groups. However, findings from the observational study PICARD[16] and other smaller retrospective studies[11-14] support earlier initiation of dialysis therapy. Nonrandomization of groups, differences in the indications for dialysis therapy initiation, and lack of inclusion of patients who recovered without dialysis therapy make interpretation of these studies difficult. A 2011 review and meta-analysis evaluating the impact of timing of dialysis therapy initiation on outcome concluded that definitive recommendations cannot be made due to lack of adequately powered randomized trials.[5]

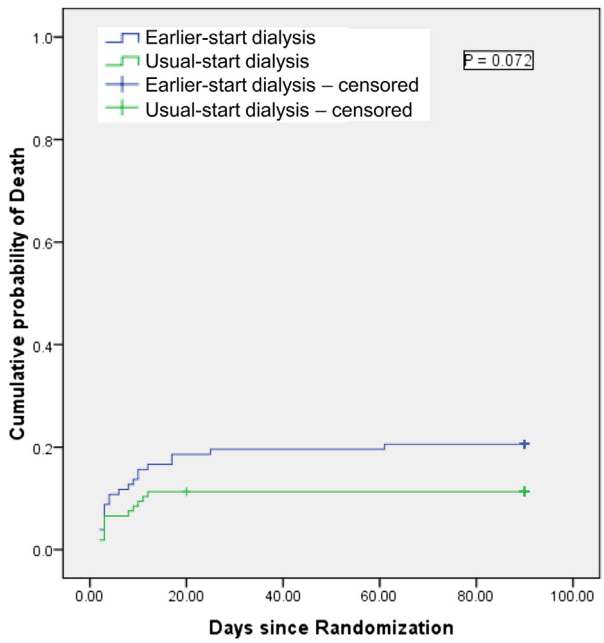

Figure 2. Kaplan-Meier estimates of the probability of death. Mortality throughout the study was similar in the earlier-start (experimental) and usual-start dialysis groups (20.5% vs 12.2% respectively; $P = 0.2$).

To our knowledge, this is the largest prospective trial evaluating the impact of timing of dialysis therapy initiation on outcome in AKI, which currently is one of the top research priorities in AKI. Specifically, data for community-acquired AKI are lacking.

Because the exact timing of AKI onset is impossible to predict if it is acquired outside the hospital, we chose to assign patients to a strategy of earlier- or usual-start dialysis rather than timing days from randomization or admission. Optimum conservative management until dialysis in the intervention arm and to delay the need of dialysis therapy initiation in the control arm was provided. This included a comprehensive approach involving a team of renal nurses, dieticians, and physicians and involved thorough clinical evaluation and treatment of volume status, hyperkalemia, metabolic acidosis, and nutrient intake. Eighteen of 106 (17.0%) participants in the control group recovered without dialysis treatment.

Earlier initiation of dialysis therapy significantly delayed the onset of recovery of kidney function. Several factors might have contributed to this finding. Exposure of blood to the dialysis membrane in the extracorporeal circuit upregulates adhesion molecules, activates leukocytes and complements pathways,

Table 3. Primary and Secondary Outcomes

Outcome	Earlier-Start Dialysis	Usual-Start Dialysis	RR or Difference[a] (95% CI)	*P*
Primary outcomes[b]				
In-hospital mortality	21/102 (20.5%)	13/106 (12.2%)	1.67 (0.88 to 3.17)	0.2
Dialysis dependence at 3 months	5/102 (4.9%)	5/106 (4.7%)	1.04 (0.29 to 3.70)	0.9
Other outcomes				
Time to recovery of kidney function[c] (d)	6.63 ± 5.71	4.70 ± 3.48	1.77 (0.39 to 3.47)	0.02
Renal failure–free days[d]	83	86	−3 (−4.06 to −1.94)	<0.001
Bleeding	10 (9.8%)	8 (7.6%)	+0.02 (−0.05 to 0.1)	0.8
Catheter-related bacteremia	4 (3.9%)	3 (2.8%)	+0.01 (−0.04 to 0.07)	0.1
Hypotension during dialysis	7 (6.8%)	7 (6.7%)	+0.001 (−0.07 to 0.07)	0.1
Requirement of blood transfusion	28 (27.4%)	25 (24.0%)	+0.03 (−0.08 to 0.15)	0.7

Abbreviations: CI, confidence interval; RR, relative risk.

[a]RR is for earlier-start versus usual-start; difference (mean or median or proportion difference) is earlier-start value less usual-start value.

[b]Values in groups given as number of events, number with data (percentage).

[c]In patients who received dialysis; computed from time of enrollment to last dialysis session; mean ± standard deviation.

[d]During 3-month follow-up period.

which may add to the proinflammatory milieu in these patients.[17-19] Loss of autoregulation make kidneys vulnerable to further ischemia during hemodynamic alterations of dialysis, which may perpetuate ischemic tubular damage, delaying their recovery.[20,21] Our findings caution against prophylactic initiation of dialysis therapy, and we agree with the conclusion of a systematic review on this topic that the only indications for dialysis therapy in AKI are significant volume overload refractory to diuretics, hyperkalemia, and refractory metabolic acidosis.[7] In the absence of these indications and with close clinical monitoring, initiation of dialysis therapy can be delayed safely.

Our results do not mean that one should wait for a life-threatening uremic complication to develop before initiation of dialysis therapy; close clinical and laboratory monitoring can identify patients who need dialysis early. Fifteen (14.0%) patients assigned to the control group required dialysis at a serum creatinine level <7 mg/dL, indicating the need for careful monitoring and individualization of the decision to start dialysis therapy. Several other factors, such as cause of kidney failure, catabolic state, comorbid conditions, need for blood product transfusion, and fluid balance after hospitalization, should be taken into account for this purpose. The most common indication of dialysis in our patients in the control group was anorexia, nausea attributable to uremia leading to decreased nutrient intake. Only 3 cases needed emergency initiation of dialysis therapy in this group; 2 for fluid overload and 1 for hyperkalemia.

Our study has limitations. First, our study population differs from the usual AKI population. While available data mainly involve critically ill patients with sepsis, this study predominantly involved patients with community-acquired AKI, which is the most common renal emergency in developing countries. The mean age of our study population was lower and the comorbid condition burden was less than that encountered in the West.[22] AKI associated with tropical infections (69.2%) and obstetric complications (5.7%) constituted the bulk of AKI burden in our study. Although 80.2% of the study population had at least one nonrenal organ with decreased function, overall illness severity of our study population was less than that of a typical sepsis-associated AKI population.[3,22] Also, the pattern of organ involvement is different in community-acquired versus sepsis-associated AKI. While mildly decreased hepatic function and thrombocytopenia commonly accompany tropical infections, similar abnormalities in sepsis may indicate more severe illness and associated higher mortality. Respiratory involvement in the form of acute respiratory distress syndrome was uncommon (8.5% of all participants) in our population, whereas it often is present in patients with sepsis-associated AKI and carries a worse prognosis. Given the difference in population characteristics, our findings cannot be generalized to the critically ill patients in the intensive care unit. However, our findings provide a rationale for the design of a similar trial in other clinical settings with AKI.

A second limitation is that we used intermittent dialysis and not continuous renal replacement therapy as the modality of renal replacement therapy in most of our patients. However, we were able to successfully use it in all study participants with close monitoring, and with technique modification in hemodynamically unstable patients. The VA NIH (Veterans Administration National Institutes of Health) trial[22] has previously shown that it is possible to use intermittent dialysis even in hemodynamically unstable patients.

Other treatment limitations also are worthy of consideration. Of note, we could monitor the dose of dialysis in only 83 (45.8%) studied patients. Also, we had the team of dedicated nephrology staff—dietitian, nurses, and physicians—available 24 hours per day who could carry out expectant management of AKI and decide whether to initiate dialysis therapy whenever needed. Thus, training of health care professionals will be required before application of these findings in different settings.

A final limitation to note is that analysis of time to kidney function recovery has limitations. We restricted this analysis to only patients who received dialysis because of the inability to objectively assess time to recovery in participants who recovered without dialysis.

Nonetheless, because confounding by significant comorbid conditions and extrarenal organ dysfunction in intensive care unit–acquired AKI makes it difficult to evaluate the effect of treatment strategies on mortality, community-acquired AKI provides a unique model to precisely define the effect of dialysis strategies on outcome. Difficulty quickly identifying patients with AKI who will need dialysis significantly limits the design of timing trials, which potentially may be facilitated by the availability of scores incorporating clinical severity and biomarkers.[23]

In conclusion, this randomized controlled trial does not support the use of earlier-start dialysis in patients with community-acquired AKI and suggests that its use may be associated with delayed recovery of kidney function. Large multicenter studies to evaluate the effect of timing strategies on outcome of AKI in intensive care settings are needed.

ACKNOWLEDGEMENTS

We thank all study participants and their families; Drs Nandkishore Kabra, Pratap Jadhav, and Nitya Gogtay for statistical advice; Mansi Bapat and team for nutritional evaluations and interventions; Harinakshi Rai for laboratory support; and Kiran Chitore and team for technical support for dialysis.

Support: This study was not funded by any agency; dialysis treatments and evaluation were partly supported by the Department of Nephrology of KEM Hospital.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

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