Survival by Dialysis Modality in Critically Ill Patients with Acute Kidney Injury

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Among critically ill patients, acute kidney injury (AKI) requiring dialysis is associated with mortality rates generally in excess of 50%. Continuous renal replacement therapies (CRRT) often are recommended and widely used, although data to support its superiority over intermittent hemodialysis (IHD) are lacking. Data from the Program to Improve Care in Acute Renal Disease (PICARD), a multicenter observational study of AKI, were analyzed. Among 398 patients who required dialysis, the risk for death within 60 d was examined by assigned initial dialysis modality (CRRT [*n* = 206] *versus* IHD [*n* = 192]) using standard Kaplan-Meier product limit estimates, proportional hazards ("Cox") regression methods, and a propensity score approach to account for selection effects. Crude survival rates were lower for patients who were treated with CRRT than IHD (survival at 30 d 45 *versus* 58%; *P* = 0.006). Adjusted for age, hepatic failure, sepsis, thrombocytopenia, blood urea nitrogen, and serum creatinine and stratified by site, the relative risk for death associated with CRRT was 1.82 (95% confidence interval 1.26 to 2.62). Further adjustment for the propensity score did not materially alter the association (relative risk 1.92; 95% confidence interval 1.28 to 2.89). Among critically ill patients with AKI, CRRT was associated with increased mortality. Although the results could reflect residual confounding by severity of illness, these data provide no evidence for a survival benefit afforded by CRRT. Larger, prospective, randomized clinical trials to compare CRRT and IHD in severe AKI are needed.

J Am Soc Nephrol 17: 3132–3138, 2006. doi: 10.1681/ASN.2006030268

Acute kidney injury (AKI) frequently complicates critical illness and is associated with considerable mortality and morbidity. When severe enough to require dialysis, mortality rates in excess of 50% have been reported in most studies (1–4). Since its introduction in the late 1970s (5), continuous renal replacement therapy (CRRT), including hemofiltration and hemodiafiltration, has gained widespread acceptance in the treatment of dialysis-requiring AKI (6–10). Several clinical trials have demonstrated beneficial effects of CRRT over intermittent hemodialysis (IHD) on hemodynamic stability, solute clearance, and ultrafiltration capacity (11–16). Direct comparisons of CRRT and IHD using observational data are problematic, because patients who are hemodynamically unstable are more likely to be treated with CRRT. Attempts to account for underlying severity of illness and comorbidity have yielded disparate conclusions (17,18). Results from underpowered randomized clinical trials of CRRT and IHD have been limited and equivocal (19–21).

This controlled study by Cho and colleagues on the benefits of continuous versus *intermittent dialysis in treating acute kidney injury relates to a Mini-Review by Van Biesen* et al. *in this month's issue of* CJASN *(pp. 1314–1319) that discusses how acute kidney injury is currently defined and the use of the RIFLE criteria.*

In this study, we analyzed the subcohort of patients from the Program to Improve Care in Acute Kidney Disease (PICARD) who required dialysis (*n* = 398), evaluating clinical characteristics and outcomes that were associated with the initial assigned dialysis modality (CRRT *versus* IHD). We hypothesized that unadjusted results would show a survival advantage to IHD and that results adjusted for confounding and selection effects would show no significant difference between assigned modality groups.

Materials and Methods

Study Participants

The PICARD network is composed of five academic medical centers in the United States: University of California San Diego (Coordinating Center), Cleveland Clinic Foundation (CCF), Maine Medical Center, Vanderbilt University, and University of California San Francisco. During a 31-mo period (February 1999 to August 2001), all patients who

Received March 24, 2006. Accepted August 21, 2006.

Published online ahead of print. Publication date available at www.jasn.org.

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ISSN: 1046-6673/1711-3132

were consulted for AKI in the intensive care unit (ICU) were evaluated by PICARD study personnel for potential study participation. Given the large number of ICU beds at CCF, one in six patients with AKI were randomly assigned for possible study inclusion to avoid single-center overrepresentation. For the PICARD study, AKI was defined as an increase in serum creatinine ≥0.5 mg/dl with baseline serum creatinine <1.5 mg/dl or an increase in serum creatinine ≥1.0 mg/dl with baseline serum creatinine ≥1.5 mg/dl and <5.0 mg/dl. Patients with a baseline serum creatinine ≥5.0 mg/dl were not considered for study inclusion. Baseline chronic kidney disease was defined as an estimated GFR <30 ml/min per 1.73 m^2 (corresponding to National Kidney Foundation Kidney Disease Outcomes Quality Initiative [K/DOQI] stage IV chronic kidney disease).

A detailed description of PICARD inclusion and exclusion criteria, data elements, and data collection and management strategies are described elsewhere (22). Patients who were contacted by study personnel and who signed (or whose proxy signed) informed consents were enrolled in the study cohort. The reason for nonenrollment was determined for patients who did not sign informed consent, although no additional data were collected for privacy considerations (23). The Committees on Human Research at each participating clinical site approved the study protocol and informed consent. The timing of initiation, modality, frequency, and dose of dialysis were determined by the treating physician with no influence from study personnel.

Statistical Analyses

Continuous variables were expressed as means ± SD or median and compared (by assigned modality) using *t* test or the Wilcoxon rank sum test, where appropriate. Categorical variables were expressed as proportions and compared with the Cochran-Mantel-Haenszel χ^2 test or Fisher Exact test. We examined the time to death within 60 d using the Kaplan-Meier product limit estimate, and compared survival curves with the log rank test.

We created a propensity score using assigned modality as the dependent variable (24). Using multiple logistic regression, we considered as candidate variables all demographic, clinical, and laboratory factors that were associated with assigned modality on univariate analysis. We retained all variables with $P < 0.20$ in the propensity score. We then ranked patients by their estimated propensity score and grouped patients into tertiles. By considering outcomes within propensity categories, comparisons are closer to what might be expected if assignment were randomized (25). Discrimination of the propensity score model was assessed using the area under the receiver operating characteristic curve (26), with higher values indicating better discrimination. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test (27). The Hosmer-Lemeshow test compares model performance (observed *versus* expected) across deciles of risk to test whether the model is biased (*i.e.*, performs differentially at the extremes of risk). A nonsignificant value for the Hosmer-Lemeshow χ^2 suggests an absence of such bias.

Proportional hazards ("Cox") regression was used to determine the associations of modality assignment and other covariates measured at the time of dialysis initiation, stratified by site (28). We included as covariates factors that were associated with mortality on the day of dialysis initiation (29). Hazard ratios (relative risks [RR]) and 95% confidence intervals (CI) were calculated from model parameter coefficients and SE, respectively. Plots of log (−log [survival rate]) against log (survival time) were performed to establish the validity of the proportionality assumption (30). We fitted models adjusted for covariates only, the propensity score only, and a combination of covariates plus the propensity score. We also fitted models within tertiles of propensity score to evaluate the consistency of the results across the range of likelihood of modality assignment.

Two-tailed $P < 0.05$ was considered significant. Statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

Results

Of the 398 patients who required dialysis for severe AKI, 206 started on CRRT and 192 started on IHD. Table 1 shows demographic, historical, clinical, and selected laboratory values by initial dialysis modality. Modality assignment differed significantly by site: Initial assignment to CRRT ranged from 27% at Vanderbilt University to 61% at CCF and University of California San Diego. In general, patients who were assigned to CRRT had more organ system failure and more significant physiologic disturbances, including hypotension and tachycardia. Fewer than half of all patients had a pulmonary artery (PA) catheter in place on the day of dialysis initiation, although PA catheter use was more common, as expected, among patients who were started on CRRT (96 [47%] of 206 *versus* 43 [22%] of 192; $P < 0.0001$). Among patients with a PA catheter, there were no significant differences in mean PA systolic ($P = 0.17$) or diastolic ($P = 0.89$) pressure or pulmonary capillary wedge pressure ($P = 0.54$) by initial dialysis modality.

Independent Predictors of Modality Assignment

Older patients (odds ratio [OR] 0.81; 95% CI 0.68 to 0.97 per decade) and nonwhite patients (OR 0.50; 95% CI 0.26 to 0.98) were less likely to be treated with CRRT as initial dialysis modality, as were patients with higher blood urea nitrogen (OR 0.94; 95% CI 0.88 to 1.00 per 10 mg/dl), higher serum creatinine (OR 0.85; 95% CI 0.74 to 0.98 per mg/dl), higher systolic BP (OR 0.70; 95% CI 0.61 to 0.81 per 10 mmHg), and no PA catheter use (OR 0.38; 95% CI 0.20 to 0.73). Independent predictors of initial assignment to CRRT included respiratory organ system failure (OR 2.22; 95% CI 1.21 to 4.06) and a positive fluid balance determined by intake and output measurements (OR 1.26; 95% CI 1.11 to 1.42 per 1 L positive balance). Cardiovascular (OR 1.62; 95% CI 0.89 to 2.95; $P = 0.11$) and hematologic (OR 1.65; 95% CI 0.86 to 3.18; $P = 0.13$) organ system failure were included in the propensity score equation on the basis of the more liberal *P*-value criterion ($P < 0.2$) but were not significantly ($P < 0.05$) associated with modality assignment after adjustment for the variables noted above. The area under the model's receiver operating characteristic curve was 0.87, indicating very good discrimination in determining modality assignment. The model was well calibrated (Hosmer-Lemeshow χ^2, $P = 0.64$). Table 2 shows variables that were included in the propensity score, along with parameter coefficients, SE, and levels of statistical significance.

Initial Dialysis Modality and Mortality

Crude survival rates were lower for patients who were treated with CRRT than with IHD (survival at 30 d 45 *versus* 58%; log rank $P = 0.006$). Adjusted for age, hepatic failure, sepsis, thrombocytopenia, blood urea nitrogen, and serum creatinine and stratified by site, the RR of death associated with CRRT was 1.82 (95% CI 1.26 to 2.62). Further adjustment for the

Table 1. Patient characteristics at dialysis initiation by modality[a]

Parameter	CRRT (n = 206)	IHD (n = 192)	P
Mean age (yr)	54.6	60.8	<0.0001
Female (%)	40	45	0.31
Race/ethnicity (%)			0.60
white	80	77	
black	6	8	
Asian	8	8	
Hispanic	5	5	
other	1	2	
History of CKD, stage IV or above (%)	32	43	0.03
Surgery pre/at ICU admission (%)	49	45	0.42
History of hypertension (%)	43	54	0.02
History of diabetes (%)	25	29	0.38
History of COPD (%)	13	18	0.16
History of heart failure (%)	26	25	0.87
History of coronary artery disease (%)	25	35	0.04
No. of organ systems failed (median [IQR])	3 (3 to 4)	3 (2 to 4)	<0.0001
Central nervous system failure (%)	31	15	0.0007
Liver failure (%)	46	31	0.005
Hematologic failure (%)	36	24	0.013
Cardiovascular failure (%)	51	41	0.08
Respiratory failure (%)	83	66	0.0004
Mechanical ventilation (%)	70	47	<0.0001
Acute lung injury (%)	55	34	<0.0001
ARDS (%)	39	20	<0.0001
Sepsis or septic shock (%)	46	31	0.002
Mean heart rate (per min)	102	90	<0.0001
Tachycardia (%)	55	28	<0.0001
Mean systolic BP (mmHg)	105	124	<0.0001
Mean diastolic BP (mmHg)	53	60	<0.0001
Mean arterial BP (mmHg)	70	81	<0.0001
Mean pulse pressure (mmHg)	52	64	<0.0001
Mean temperature (°C)	37.1	36.7	0.004
Median urine output (ml)	415	423	0.44
Oliguria (≤400 ml/d; %)	51	52	0.91
Mean respiratory rate	21	20	0.51
Median total bilirubin (mg/dl)	3.3	1.6	0.012
Mean creatinine (mg/dl)	4.0	5.1	<0.0001
Mean BUN (mg/dl)	77	95	<0.0001
Mean platelets (1000/mm^3)	131	164	0.006
Thrombocytopenic (<100 × 10^6/L; %)	45	30	0.002
Mean pH	7.34	7.34	0.93
Mean potassium (mEq/L)	4.6	4.6	0.42
Mean bicarbonate (mEq/L)	20.3	20.4	0.89
Mean leukocyte (1000/mm^3)	14.9	14.9	0.97
Mean hemoglobin (g/dl)	10.0	10.2	0.40

[a]ARDS, adult respiratory distress syndrome; BUN, blood urea nitrogen; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRRT, Continuous renal replacement therapy; IHD, intermittent hemodialysis; IQR, interquartile range.

propensity score did not materially alter the association (RR 1.92; 95% CI 1.28 to 2.89). In other words, using the wide array of observed covariates that were collected in PICARD, the increase in risk among patients who were assigned to CRRT could not be explained by confounding or selection effects.

Within tertile 1 (patients whose clinical characteristics pre-

Table 2. Propensity score model for assignment to CRRT[a]

Parameter	df	Estimate	SE	Wald χ^2	*P*
Intercept	1	−0.0441	4.8766	0.0001	0.9928
UCSF	1	−0.3623	0.4285	0.7150	0.3978
CCF	1	0.0497	0.4751	0.0110	0.9167
VU	1	−2.2034	0.5090	18.7424	<0.0001
MMC	1	−1.4624	0.5981	5.9796	0.0145
Nonwhite	1	−0.6915	0.3406	4.1225	0.0423
Age	1	−0.2101	0.0936	5.0398	0.0248
CV failure	1	0.4824	0.3054	2.4959	0.1141
Hematologic failure	1	0.5010	0.3344	2.2445	0.1341
Respiratory failure	1	0.7965	0.3082	6.6764	0.0098
Systolic BP	1	−0.3514	0.0705	24.8269	<0.0001
Temperature	1	0.1907	0.1294	2.1729	0.1405
BUN	1	−0.0659	0.0343	3.6868	0.0548
Creatinine	1	−0.1660	0.0725	5.2344	0.0221
No PA catheter	1	−0.9641	0.3315	8.4567	0.0036
I/O balance	1	0.2278	0.0624	13.3078	0.0003

[a]Age per 10 yr; systolic BP per 10 mmHg; temperature per °C; BUN per 10 mg/dl; creatinine per mg/dl; I/O balance per 1000 ml positive; University of California San Diego referent site. CCF, Cleveland Clinic Foundation; CV, cardiovascular; I/O balance, intake output balance; MMC, Maine Medical Center; PA, pulmonary artery; UCSF, University of California San Francisco; VU, Vanderbilt University.

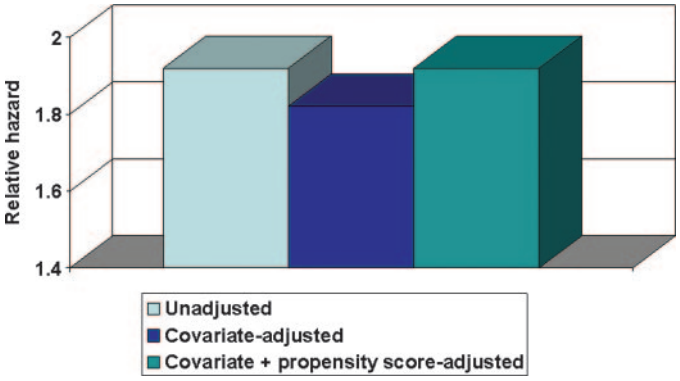

Figure 1. Mortality within 60 d after acute kidney injury requiring dialysis: Continuous renal replacement therapies *versus* intermittent hemodialysis.

dicted a low likelihood of assignment to CRRT), 22 (17%) patients started CRRT and 110 (83%) started IHD. Within tertile 2, 71 (53%) patients started CRRT and 62 (47%) started IHD. Within tertile 3 (patients whose clinical characteristics predicted a high likelihood of assignment to CRRT), 113 (85%) patients started CRRT and 20 (15%) started IHD. Within all three tertiles, the risks for death were nominally higher with assignment to CRRT, although there was no significant difference in tertile 2, the group in which patients' characteristics did not clearly predict one modality or another. The risks that were associated with initial assignment to CRRT within the three tertiles were as follows: Tertile 1 RR 2.88, 95% CI 1.47 to 5.66; tertile 2 RR 1.39, 95% CI 0.75 to 2.58; and tertile 3 RR 2.90, 95% CI 1.06 to 7.94).

Discussion

A relatively large fraction of critically ill patients with severe AKI require dialysis during an ICU stay. The traditional approach to management is IHD, usually delivered three times per week for several hours per session, not unlike maintenance hemodialysis that is used in patients with ESRD. In the acute setting, peritoneal dialysis has fallen out of favor as a result of infectious and other (*e.g.*, respiratory and metabolic) complications. In the past two decades, CRRT, including continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration, and continuous venovenous hemodiafiltration, have gained in popularity and usage, particularly for the treatment of hemodynamically unstable patients. Although several small studies have suggested improved physiologic parameters in response to CRRT relative to IHD (11–16), these data are not definitive. Evaluation of outcomes that are associated with modality choice are hampered by residual confounding and selection bias, because most programs tend to use CRRT for more severely, acutely ill patients (18,22,30). For example, Swartz *et al.* (18) compared mortality rates by modality assignment in 349 patients with dialysis-requiring AKI during 1995 through 1996 at the University of Michigan. The odds for death with assignment to CRRT was roughly twice that of IHD; however, after exclusion of patients with hypotension (systolic BP <90 mmHg), severe hyperbilirubinemia (>15 mg/dl), and a very short period of renal replacement (<48 h), the risk for death that was associated with CRRT no longer was significantly higher (RR 1.09; 95% CI 0.67 to 1.80). In a re-analysis of this cohort, Martin *et al.* (31) found that the CRRT-treated patients had an unexpected higher mortality, particularly in patients who were categorized as low risk by the Cleveland Clinic score. In a follow-up study during 2000 through 2001

($n = 383$), Swartz *et al.* (32) found an increase in the risk for death with CRRT on unadjusted analysis and no significant difference after adjustment for comorbidity and severity of illness. Subgroup analyses were conducted, some of which suggested favorable trends with CRRT, although none was statistically significant and there was no consideration of multiple comparisons. Chang *et al.* (33) described 148 South Korean ICU patients with dialysis-requiring AKI. As expected, patients who were treated with continuous venovenous hemodiafiltration were more severely ill and had significantly lower survival rates (21 *versus* 46%; $P = 0.002$). On subgroup analysis, patients with APACHE III scores >103 and more than three organ failures had nominally higher survival with CRRT. Other observational studies have demonstrated conflicting findings, examining mortality and renal recovery after dialysis-requiring AKI.

Several randomized clinical trials have compared CRRT and IHD in severe AKI, although none has been adequately powered. In the largest randomized clinical trial, Mehta *et al.* (19) compared CRRT and IHD in 166 critically ill patients with severe AKI and found a significantly higher ICU mortality rate in patients who were randomly assigned to CRRT (60 *versus* 42%; $P = 0.02$). However, despite randomization, patients who were assigned to CRRT were significantly more likely to have liver failure and had a higher overall severity of illness, as determined by APACHE III score. Adjustment for these factors attenuated the increased risk that was attributed to CRRT (OR 1.6; 95% CI 0.7 to 3.3). More recently, two (underpowered) randomized clinical trials that compared CRRT and IHD failed to show a significant difference in survival by dialysis modality (21,34). Meta-analyses also have been conducted and have concluded that there is no significant difference in survival by modality, although study quality and heterogeneity were not optimal (17,20).

This study extends previous work in this area using observational data by incorporating multiple sites, a larger sample size, multivariable regression analysis, and the propensity score approach to address residual confounding and selection effects. Although data collection in PICARD generally was comprehensive, all data elements were not collected in all patients (*e.g.*, data from PA catheters), largely as a result of differences in clinical practice among and within sites. In addition, we could not control for other aspects of dialysis care (*e.g.*, urea or other solute clearance) and other co-interventions that were not randomly assigned.

Although propensity scores cannot fully adjust for residual confounding and selection bias, the method has been widely used in observational studies that have examined the effectiveness of various interventions in nephrology and critical care. As with other conditions for which there is uncertainty as to the optimal therapeutic approach, there tends to be wide variation in practice by institution and individual physician in the choice of modality for dialysis-requiring AKI. A propensity score can help account for this variation, which may be unrelated to severity of illness or other biologic factors that influence outcomes. We previously used propensity scores to estimate the effects of the timing of consultation (35) and the use of diuretics (36) and dopamine (37) in AKI. Propensity scores also were used in studies that evaluated the effectiveness of albumin administration (38), blood transfusion (39), and right heart catheterization (40) in the critically ill.

It should be emphasized that the multivariable analyses (with or without the propensity score) support the crude (unadjusted) results that demonstrate an increased risk for death among patients who are assigned to CRRT. In the "naïve" multivariable analyses (not adjusted for the propensity score), we adjusted for significant predictors of death at dialysis initiation. Inclusion of other covariates (*e.g.*, mechanical ventilation, clinical criteria for acute lung injury or adult respiratory distress syndrome, systolic BP) in addition to or in place of the core model covariates did not extinguish the association between assignment to CRRT and mortality. Moreover, when considering factors that were associated with assignment to CRRT but were not significant predictors of death (*e.g.*, use of PA catheter, intake-output balance), we observed risk ratios in the same direction and of the same magnitude as in the unadjusted analysis.

There are several important limitations to this study. First, propensity scores can adjust only for the associations among observed covariates and the chosen treatment or strategy. Other unobserved covariates could influence the likelihood of treatment, and there is no guarantee that the correlation among observed and unobserved covariates is sufficiently high to account adequately for this deficiency. Second, the study was conducted at five academic tertiary care medical centers. Therefore, results may not be fully generalizable to other medical centers, particularly those where CRRT is applied less frequently. Third, we collected no information on long-term survival, functional status, or dialysis dependence for patients who survived hospitalization. Future observational studies and clinical trials in AKI should attempt to understand the long-term effects of dialysis-requiring AKI episodes. Finally, although an extensive number of variables were collected and were done so serially during patients' ICU stays, we could not capture every aspect of intensive care, so residual confounding by severity of illness is likely.

Although the major results described here could reflect residual confounding, the possibility that CRRT might cause harm still should be considered. CRRT requires continuous anticoagulation; may remove water-soluble vitamins, drugs (including antibiotics), and amino acids; and may result in clearance and/or adsorption of a variety of known and unknown modulators of the inflammatory and counterinflammatory response. Moreover, despite technological advances, it remains a complex intensive therapy that requires considerable nursing and physician expertise. Given the high incidence of AKI in the ICU and the morbidity, associated mortality, and costs that are associated with dialysis-requiring AKI, better evidence is needed to guide AKI treatment strategies.

There are numerous examples in which drugs, devices, and technologies have been introduced into medical practice on the basis of a sound rationale, yet subsequent clinical practice and research demonstrate that the use of these technologies is associated with no benefit or even harm. Recent examples include

the use of PA catheters in the ICU (41,42), the use of certain antiarrhythmic agents in an attempt to prevent sudden cardiac death (43), and the use of selected inotropes and vasodilators in the treatment of congestive heart failure (44). When the results of the current observational study on dialysis-requiring AKI in the ICU are integrated with other observational studies and clinical trials, there is no evidence of the superiority of CRRT over IHD and some evidence to support possible inferiority.

At this time, the data that are presented here should be considered hypothesis generating and not definitive and should not be used to change clinical practice. However, in the context of increasing CRRT use, it now is imperative that a randomized clinical trial of adequate power be conducted to determine whether mortality rates that are associated with severe dialysis-requiring AKI can be reduced with the use of CRRT, IHD, or a hybrid technique, such as slow low-efficiency dialysis. Such a study will need to include patients who could be treated successfully with either modality (comparing "apples and apples"), potentially excluding patients with severe hypotension and hemodynamic instability, who may be poor candidates for traditional IHD, and should standardize key elements of therapy, including the timing of initiation, dosage of dialysis, and the expertise of personnel delivering the therapy.

Acknowledgments

This study was supported by the following research grants from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: RO1-DK53412, RO1-DK53411, RO1-DK53413, and R33-DK67645.

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