Impact of Dialysis Adequacy on the Mortality and Morbidity of Anuric Chinese Patients Receiving Continuous Ambulatory Peritoneal Dialysis

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Abstract. Dialysis adequacy has a major impact on the outcome of continuous ambulatory peritoneal dialysis (CAPD) patients. However, most studies on peritoneal dialysis adequacy have focused on patients with significant residual renal function. The present study examined the effect of dialysis adequacy on anuric CAPD patients. A single-center prospective observational study on 140 anuric CAPD patients was performed. These patients were followed for 22.0 ± 11.9 mo. Dialysis adequacy and nutritional indices, including Kt/V, creatinine clearance (CCr), protein equivalent nitrogen appearance, percentage of lean body mass, and serum albumin level were monitored. Clinical outcomes included actuarial patient survival, technique survival, and duration of hospitalization. In the study population, 64 were male, 36 (25.7%) were diabetic, and 59 (42.1%) were treated with 6 L exchanges per day. The body weight was 59.2 ± 10.2 kg. Average Kt/V was 1.72 ± 0.31, and CCr was 43.7 ± 11.5 L/wk per 1.73m². Two-yr patient survival was 68.8%, and technique survival was 61.4%. Multivariate analysis showed that DM, duration of dialysis before enrollment, serum albumin, and index of dialysis adequacy (Kt/V or CCr) were independent factors of both patient survival and technique survival. It was estimated that for two patients who differed only in weekly Kt/V, a 0.1 higher value was associated with a 6% decrease in the RR of death (P < 0.05; 95% confidence interval, 0.92 to 0.99). Serum albumin and CCr were the only independent factors that predicted hospitalization. It was found that even when there is no residual renal function, higher dialysis dosage is associated with better actuarial patient survival, better technique survival, and shorter hospitalization. Dialysis adequacy has a significant impact on the clinical outcome of CAPD patients, and the beneficial effect is preserved in anuric patients as well as in an ethnic group that has a low overall mortality.

Continuous ambulatory peritoneal dialysis (CAPD) is the treatment modality of 14% of the world’s dialysis population (1). The adequacy of peritoneal dialysis has a profound impact on mortality and morbidity of CAPD patients (2–6). Although Chinese dialysis patients have better overall outcome (7,8), dialysis adequacy remains an independent predictor of mortality and morbidity of CAPD patients in this ethnic group (9).

However, most studies on peritoneal dialysis adequacy have focused on patients with significant residual renal function. In the CANUSA study, which enrolled only new CAPD patients, nutritional parameters actually worsen after the first 6 mo of the study period, probably secondary to gradual decline of residual renal function (10). The maintenance of adequate dialysis is challenging for patients with little urine output; utilization of higher daily exchange volume becomes inevitable. Although renal and peritoneal clearances have often been considered equivalent, this assumption has never been proved (11–13). Previous studies from our group suggested that this assumption might not be valid (9,14).

The independent effect of peritoneal clearance on patient outcome can be examined in anuric CAPD patients. Nevertheless, this approach is practically difficult in most countries because hemodialysis is a readily available alternative for end-stage renal disease (ESRD) patients. Conversely, CAPD is the first-line renal replacement therapy for all ESRD patients in our locality (8). Patients are switched to long-term hemodialysis only when they have ultrafiltration failure or peritoneal sclerosis. Although this policy may not be ideal, it provides an excellent opportunity for us to examine the effect of dialysis adequacy on the clinical outcome of a large unselected group of anuric CAPD patients.

Materials and Methods

Patient Selection

We enrolled 140 anuric CAPD patients of our center from September 1995 to December 1998. Anuria was defined as no appreciable urine output. Forty-four patients (31.4%) had been participants of our
previous prospective study (9) and were enrolled after they completed the previous study. The other 96 patients (68.6%) were enrolled separately, within 6 mo after they became anuric. We did not enroll patients who were unlikely to survive for 6 mo; the aim of this was to exclude patients who had obviously life-threatening conditions, such as disseminated malignancy and severe organ disease (lung and liver), and those who were in so critical a condition that it precluded meaningful dialysis adequacy study.

Informed consent was obtained. The dialysis regimen was that prescribed by the individual patient’s nephrologist and has been described previously (8). Basically, three 2-L daily exchanges were routinely prescribed during commencement of CAPD, and daily exchange volume was increased only when there was poor ultrafiltration that failed to improve with hypertonic dialysate. The record of dialysis adequacy and nutritional data, except serum albumin level, were kept by a central database for convenience of management and separate from patients’ clinical records. They were available to the clinician upon request. However, prescription and alteration of dialysis regimen were based on clinical judgment and not the numeric adequacy data.

Data Collection

Baseline data including age, gender, underlying renal disease, CAPD regimen, connection system, duration on dialysis before enrollment, body height, requirement of helper for dialysis exchanges, hepatitis B status, presence of diabetes mellitus (DM), and history of cardiovascular disease (CVD) were obtained. CVD was defined as angina, class III to IV congestive heart failure, a history of myocardial infarction, cerebrovascular accident, including transient cerebral ischemia, or amputation for vascular disease; intermittent claudication of lower limb was not counted.

Clearance studies were performed at least yearly by 24-h dialysate collections. The method of clearance study was reported previously (9). Briefly, the daily drained volume of dialysate was mixed, measured volumetrically, and sent for measurement of urea, creatinine, and glucose concentrations. At the end of the 24-h collection, body weight was measured and a blood sample was obtained for measurement of hemoglobin, serum urea, creatinine, and albumin concentrations. Serum albumin level was measured by bromocresol purple method. When there was an acute medical problem such as peritonitis, this study was obtained at least 1 mo after resolution of the problem.

Adequacy of dialysis was estimated by measurement of weekly Kt/V and weekly creatinine clearance (CCr) by standard methods (15). Creatinine concentration in dialysate was corrected for interference by glucose according to reference formula determined in our laboratory (16). Protein equivalent nitrogen appearance (PNA) was calculated by the methods described by Randerson et al. (17) and normalized to standard body weight (total body water/0.58). Total body water (V) was determined by the Watson’s formula (18). Percentage of lean body mass (%LBM) was determined from creatinine kinetics according to Forbes and Brunining (19). Serum albumin concentration, %LBM, and PNA were taken as markers of nutrition.

Clinical outcomes in this study included actuarial patient survival, technique survival, and days of hospitalization for all causes. Transplantation and loss of follow-up were censored observations for patient survival. Patient deaths after conversion to hemodialysis were counted as events. Technique survival was defined as patient remaining alive and on CAPD. Duration of hospitalization was normalized to days per month of follow-up.

Statistic Analyses

Statistical analysis was performed by SYSTAT 7.0 for Windows software (SPSS Inc., Chicago, IL). Results were expressed as mean ± SD unless otherwise stated. Serial changes of dialysis adequacy and nutritional parameters during the study period were compared with the baseline values and examined by ANOVA for repeated measures. All probabilities were two-tailed.

The Cox proportional hazards model was used for statistical analysis of patient and technique survival (20). Similar to the CANUSA study, nutritional indices (serum albumin, PNA, and %LBM) and dialysis adequacy indices (Kt/V and CCr) were treated as time-dependent covariate (6,21,22). In essence, this means that we attribute a clinical event such as death to the most recent clearance measurement performed. Transplantation and loss of follow-up but not conversion to hemodialysis were counted as censored observations for patient survival analysis. Loss of follow-up was counted as censored observation for technique survival analysis. Baseline demographic variables used for modeling were age at enrollment, gender, duration of dialysis before enrollment, diabetic status, hepatitis B status, and CVD. Backward stepwise elimination was applied to remove insignificant variables. Then the two indices of dialysis adequacy (Kt/V and CCr) were added separately to this model. PNA and %LBM each were added for model estimation similarly. Because a correlation matrix for parameters of nutritional status showed only modest correlations between serum albumin and other adequacy and nutritional indices, serum albumin level was added independently for all model estimations. The likelihood ratio test (21) was used to determine whether the addition of a variable to a model added significantly to that model.

The log-linear model was used to analyze hospitalization (23) because the data were significantly skewed. The dependent variable was the number of days hospitalized per month of follow-up. The baseline demographic variables used for analysis were similar to those for survival analysis. Dialysis adequacy indices and nutritional parameters were then added for model estimation.

Results

There were 140 patients enrolled, with a total follow-up period of 3080 patient-months. Forty-four patients (31.4%) were participants of our previous study on survival of Chinese CAPD patients (9). The average duration of study follow-up was 22.0 ± 11.9 mo (median, 20 mo). The demographic and baseline clinical characteristics are summarized in Table 1. The mean daily exchange volume was 7.4 ± 1.4 L; 59 patients (42.1%) had 6 L/d, 63 patients (45.0%) had 8 L/d, and 18 patients (12.9%) had 10 L/d dialysis exchange.

The baseline and follow-up values for adequacy of dialysis and nutritional status are summarized in Table 2. There were no significant changes of Kt/V and CCr with time, as determined by repeated measure ANOVA. Serum albumin, PNA, and %LBM had a rising trend during the study period, but the result was not statistically significant.

Before multivariate analysis of clinical outcome, we examined the possible intercorrelations between dialysis adequacy and nutritional indices (Kt/V, CCr, serum albumin, PNA, and %LBM) by a correlation matrix. The result was summarized in Table 3. We found a strong correlation between Kt/V and CCr. Therefore, these two parameters were added separately for survival model estimation. For similar reason, PNA and %LBM were added separately for estimation of survival model. Serum albumin level was added independently for
model estimation because its correlations with other nutritional indices were only modest.

Actuarial Survival

During the study period, 20 patients were changed to hemodialysis, 5 received transplants, and 9 transferred to other dialysis centers. During the same period, there were 46 deaths, 7 of which occurred after the change to hemodialysis and were counted as event during survival analysis. The causes of death were CVD (21 patients), peritonitis (10 patients), nonperitonitis infections (11 patients), malignancy (2 patients), liver disease (1 patient), and accident (1 patient). The remaining 67 patients were administratively censored on December 31, 1999. Kaplan-Meier estimates of patient and technique survival are shown in Figure 1. Actuarial patient survival at 24 mo was 68.8%.

The result of the Cox proportional hazard model for actuarial patient survival is summarized in Table 4. In the top portion of Table 4, Kt/V was used as the estimate of dialysis adequacy and PNA was used as the estimate of nutritional status. In the bottom portion of Table 4, CCr was used as the estimate of dialysis adequacy and %LBM was used as the estimate of nutritional status. By multivariate analysis, the independent factors for patient survival were presence of DM, duration of dialysis before enrollment, serum albumin level, and dialysis adequacy (either Kt/V or CCr). Neither PNA nor %LBM appeared in the final survival model. It was estimated that for two patients who differed only in weekly Kt/V, a 0.1 higher value was associated with a 6% decrease in the relative risk (RR) of death (P = 0.05; 95% confidence interval [CI], 0.92 to 0.99). Similarly, it was estimated that for two patients who differed only in weekly total CCr, a 5 L/wk per 1.73m² higher value resulted in a 12% reduction in RR of death (P < 0.05; 95% CI, 0.76 to 0.99).

Technique Survival

During the study period, 20 patients were changed to long-term hemodialysis. The indications were either ultrafiltration

![Image of Kaplan-Meier survival curves]

Figure 1. Kaplan-Meier estimates of actuarial patient survival and technique survival.
Table 4. Cox proportional hazard model of patient survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Mortality Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kt/V as estimate of adequacy of dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.14</td>
<td>1.15–3.97</td>
</tr>
<tr>
<td>Duration of dialysis (↑ 1 yr)a</td>
<td>1.18</td>
<td>1.05–1.31</td>
</tr>
<tr>
<td>Serum albumin (↑ 1 g/L)</td>
<td>0.88</td>
<td>0.83–0.93</td>
</tr>
<tr>
<td>Kt/V (↑ 0.1 unit/wk)</td>
<td>0.94</td>
<td>0.92–0.99</td>
</tr>
<tr>
<td>CCr as estimate of adequacy of dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.53</td>
<td>1.40–4.55</td>
</tr>
<tr>
<td>Duration of dialysis (↑ 1 yr)a</td>
<td>1.21</td>
<td>1.07–1.34</td>
</tr>
<tr>
<td>Serum albumin (↑ 1 g/L)</td>
<td>0.88</td>
<td>0.83–0.93</td>
</tr>
<tr>
<td>CCr (↑ 5 L/wk per 1.73 m²)</td>
<td>0.88</td>
<td>0.76–0.99</td>
</tr>
</tbody>
</table>

a Before enrollment into the study.

failure after peritonitis (11 patients) or symptomatic inadequate dialysis (9 patients). Only patients who remained alive and on CAPD by the end of the study period were considered as technique survivors. With this definition, the 2-yr technique survival rate of our study patients was 61.4%.

Multivariate analysis with backward stepwise regression identified that presence of DM, duration of dialysis before enrollment, serum albumin level, and dialysis adequacy (either Kt/V or CCr) were independent factors of technique survival. When Kt/V was used for model estimation, diabetic patients had a RR of technique failure of 1.64 (95% CI, 1.02 to 2.73). The RR of technique failure associated with 1 yr longer on dialysis before enrollment, 1 g/L increase of serum albumin, and 0.1 unit increase in Kt/V were 1.13 (95% CI, 1.02 to 1.24), 0.91 (95% CI, 0.86 to 0.96), and 0.94 (95% CI, 0.92 to 0.99), respectively. The result was similar when CCr was used for model estimation. The RR associated with a 5 L/wk per 1.73 m² increase in CCr was 0.88 (95% CI, 0.78 to 0.99).

Hospitalization

There were 4116 d of hospitalization during the study period. The overall hospitalization rate was 16.0 d per year of follow-up. Thirty-one patients (22.1%) were never hospitalized during the study period, and the data were significantly skewed. Therefore, the log-linear modeling was used for multivariate regression analysis. The only independent predictors of hospitalization were low serum albumin level and low CCr. Conversely, Kt/V was not an independent variable during log-linear model estimation for hospitalization.

The RR of individual hospitalization predictor can be expressed as exponential coefficient ($e^{COEF}$), which indicates the relative time hospitalized in terms of days per month of follow-up. The $e^{COEF}$ of hospitalization associated with 1 g/L increase of serum albumin and 5 L/wk per 1.73 m² increase in CCr were 0.94 (95% CI, 0.89 to 0.99) and 0.88 (95% CI, 0.79 to 0.98), respectively.

Discussion

In this prospective cohort study of anuric Chinese CAPD patients, we examined the association of dialysis adequacy with clinical outcome by multivariate statistical analysis. We found that even when there was no residual renal function, higher dialysis “dosage” was associated with better actuarial patient survival, better technique survival, and shorter hospitalization.

The beneficial effect of dialysis adequacy has been emphasized by a number of studies (2–6). However, most of them focused on patients with significant residual renal function, which considerably confounded the total dialysis dosage (6,7). In a recent retrospective review of 115 anuric CAPD patients, Kt/V correlated with overall mortality (24). However, peritoneal clearance per se has not been proved to have an independent effect on patient survival by prospective study (12). To our knowledge, the present study represents the first prospective cohort that examines the effect of dialysis adequacy in anuric CAPD patients.

Although the term adequacy of dialysis is generally used, adequacy of solute removal may be a better alternative for the present study because we examined only the effects of urea and creatinine clearances. “Adequacy” of anything other than solute removal, which might be better provided by residual renal function, was not addressed.

It is also important to note that the present study does not prove that peritoneal and renal clearances are equivalent. It merely shows that peritoneal clearance has an independent effect on clinical outcome when there is no renal clearance. In fact, both general clinical impression and early retrospective data (13,14) suggest that renal and peritoneal clearances are not equivalent. Nevertheless, our data strongly support the as yet unproved hypothesis that with progressive loss of renal clearance, which is inevitable with time on dialysis, an increase in peritoneal dialysis dosage could lead to a better clinical outcome.

In the present study, 2-yr actuarial patient survival was 68.8% (with average Kt/V 1.73), compared with 78% in the CANUSA study (with average Kt/V 2.1) (6). However, these data are not strictly comparable because most of the patients in the CANUSA study had significant residual renal function. In both cases, the expected magnitude of benefit by increasing dialysis adequacy indices is considerable. In the present study, a 0.1 unit lower value of Kt/V is associated with a 6% increase in the RR of death, which is similar to that of the CANUSA study (6) as well as our previous study (9). A rise of Kt/V from 1.7 to 2.1 is expected to increase the 2-yr actuarial patient survival from 67.6 to 86.5% in the present study. However, the CI of relative mortality risk is wide.

In the present study, serum albumin but not PNA or %LBM was the only nutritional index that had an independent effect on clinical outcome. However, recent evidence suggests that serum albumin is more a marker of systemic inflammation rather than nutrition (25,26). The poor correlation of serum albumin level with other nutritional indices in the present study also suggested that the former did not represent nutritional status.

Although recommended by the DOQI guideline as nutritional indices (27), both PNA and %LBM were complicated by mathematical coupling with Kt/V and CCr, because all of them
were measured and calculated from the same 24-h urine and dialysate collection. As a result, the effect of nutritional status on clinical outcome was possibly omitted during multivariate analysis, when dialysis adequacy index was used simultaneously for model estimation. Because of technical difficulties in follow-up arrangement, we did not use subjective global assessment as nutritional index in the present study. As a result, it would be difficult to draw any conclusion about the effect of nutritional status from the present study.

We found that the duration of dialysis had an independent effect on clinical outcome. A similar finding has been reported by other groups (2,5), but the explanation remains speculative. One possible reason is that peritoneal dialysis is more effective in removing toxins of middle or large molecular weight, which tend to accumulate with time and cause complications (28), than conventional hemodialysis; however, compared with the kidneys, it is of course much less effective (29). However, duration of dialysis represents a surrogate marker of residual renal function in some studies (2,5), and it reflects the rate of progression of the underlying renal disease in the present one, whereas most of the patients were enrolled soon after they became anuric. All of these factors have potential implications on clinical outcome and require further study.

In the present study, we excluded patients who were unlikely to survive for 6 mo. Retrospectively, our policy might exclude malnourished patients with a small V and large Kt/V and retain larger patients with a lower Kt/V. This may, interestingly, make our conclusion more powerful.

Recent analysis of the CANUSA data found that peritoneal transport characteristic was associated with patient outcome (30). Our preliminary data on CAPD patients with residual renal function also showed that peritoneal transport characteristics correlated with hospitalization but not survival (31). Unfortunately, we did not have peritoneal transport data for the present study.

In summary, dialysis adequacy has significant impact on the clinical outcome of CAPD patients, in terms of both mortality and morbidity. The beneficial effect of dialysis adequacy is preserved in anuric patients as well as in an ethnic group that has a low overall mortality, e.g., Chinese. However, the optimal dosage of peritoneal dialysis remains to be determined. The cost-effectiveness of high-dose peritoneal dialysis and patients’ quality of life also require further study.

Acknowledgments

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