SEMINARS IN
NEPHROLOGY

Dialysis Session Length ("t") as a Determinant of the Adequacy of Dialysis

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Several studies have shown an association between the hemodialysis session length (the *t* of Kt or Kt/V) and favorable outcomes for patients on maintenance hemodialysis. In a single randomized controlled trial that systematically varied hemodialysis session length, shorter session length was associated with an increased risk for morbidity and mortality, independent of the time-averaged concentration of urea. Observational studies of dialysis session length have yielded conflicting results, although virtually all studies have confounded hemodialysis session length with hemodialysis efficiency or dose. Limited observational data from nocturnal hemodialysis programs more strongly suggest an independent beneficial effect of longer session length. In aggregate, data on the effects of hemodialysis session length are inconclusive. Future studies should evaluate hemodialysis session length independent of efficiency, and should consider the evaluation of dose by using other clearance parameters and the adequacy of ultrafiltration in addition to solute kinetics.
Semin Nephrol 25:90-95

Since its first application as a treatment for end-stage renal disease, hemodialysis session lengths have shortened considerably in the United States.[1] For example, the average prescribed treatment time (*t*) in the 1990s was roughly equivalent to the t prescribed in the shortened dialysis time arm of the National Cooperative Dialysis Study (NCDS).[2] The practice of maximizing dialyzer efficiency while shortening hemodialysis session length was popularized after publication of the results of the NCDS, which placed primary importance on urea clearance over session length as a determinant of morbidity. The practice was strengthened further by the adoption of a urea kinetics–based dialysis dose, quantified either by the urea reduction ratio (URR) or the dimensionless Kt/V_{urea}, the clearance times time (Kt) product normalized to total body water (V).[3] These quantities, derived from NCDS data, suggested that if the efficiency of clearance could be increased (eg, with enhanced dialyzer clearance and more brisk blood and dialysate flow rates), session length potentially could be shortened as long as an adequate Kt/V_{urea} could be maintained.

The trend toward shorter hemodialysis session length reversed somewhat when quality improvement programs and the publication of clinical practice guidelines focused attention on achieving URR (>65% to 70%) and Kt/V_{urea} (>1.2–1.4 per session) goals. After maximizing parameters of clearance (K), increases in delivered dose could be achieved only by lengthening time (t). Nevertheless, treatment times for US patients still are considerably shorter than for their international counterparts. In 1996, incident hemodialysis patients in the United States were prescribed an average of 3.2 hours per session.[4] In contrast, Japanese patients averaged 4.1 hours per session during the same period.[5] Data from the European Limb of the Dialysis Outcomes and Practice Patterns Study (Euro-DOPPS) indicate that European hemodialysis patients averaged 3.9 hours per session between 1998 and 2000.[6] Indeed, differences in prescribed treatment times have been proposed as one factor contributing to the higher mortality rate experienced by US end-stage renal disease patients.[5] These observations, along with the preliminary results of supraconventional dialysis techniques, which increase hemodialysis session length and/or frequency, have prompted a re-evaluation of time as an important, potentially independent determinant of dialysis adequacy.

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Supported by the ASN-ASP Junior Development Award in Geriatric Nephrology (a program supported by the Atlantic Philanthropies, the American Society of Nephrology, the John A. Hartford Foundation, and the Association of Subspecialty Professors) (M.K.) and NIH-NIDDK RO1 DK58411, RO1 DK01005 and UO1 DK03005 (G.M.C.).

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0270-9295/05/$-see front matter
doi:10.1016/j.semnephrol.2004.09.015

Table 1 Published Studies of Session Length *t* and Hemodialysis Outcomes

Study	Study Design	Number of Patients	Country	Control for URR or Kt/V_{urea}	Outcome	Superiority of Longer Time
Lowrie et al, 1981[2]*	RCT	151	United States	Yes (TAC_{urea})	Death or study withdrawal	No
Laird et al, 1983[9]*	Secondary analysis of RCT	160	United States	Yes (TAC_{urea})	Hospitalization death or study withdrawal	Borderline No
					Death, study withdrawal, or hospitalization	Yes
Lowrie et al, 1990[11]	Observational	12,099	United States	No	Death	Yes
Held et al, 1991[1]	Observational	600	United States	No	Death	Yes
Shinzato et al, 1999[16]	Observational	71,193	Japan	Yes	Death	Yes
Collins et al, 1990[12]	Observational	556	United States	Yes	Death	No
Capelli et al, 1992[15]	Observational	180	United States	Yes	Death	No
Owen et al, 1993[13]	Observational	13,473	United States	Yes	Death	No
Held et al, 1996[14]	Observational	2,311	United States	Yes	Death	No
Depner et al, 2004[24]	Secondary analysis of RCT	1,846	United States	Yes	Death	No

Abbreviation: RCT, randomized controlled trial;.
*Indicates studies reporting results for same patient cohort.

Time-Dependent Effects in Hemodialysis

To evaluate the evidence examining time t as a determinant of dialysis adequacy, it first is important to differentiate between the effects of session length and frequency on solute clearance. The clearance of a solute is determined by several factors, including its plasma concentration during dialysis, the degree to which the molecule is protein bound, the intra- versus extracellular distribution, and the molecule's weight (size) and charge. Smaller molecular weight solutes such as urea are cleared efficiently during hemodialysis, leading to a rapid decrease in their plasma concentration during a single hemodialysis session. Thus, increasing the session length has a marginal effect on the net clearance of smaller, easily diffusible molecular weight solutes, such as urea. However, for some small solutes (eg, phosphate), there is a significant rebound in plasma concentration after hemodialysis caused by delayed diffusion from sequestered intracellular compartments into the plasma (where it becomes accessible to the dialyzer). For such substance, increasing the session length will enhance solute clearance significantly. In contrast to session length, frequency has a significant effect on urea kinetics owing to the effects of urea generation in the interdialytic interval. Increasing the frequency of hemodialysis decreased the peak and time-average concentration of urea (TAC_{urea}).[7,8]

In contrast, the removal of larger solutes is limited by diffusion across the dialyzer membrane. Because of relatively inefficient removal during hemodialysis, the plasma concentration of larger solutes remains high during dialysis; therefore, their net clearance is proportional to total treatment time. Thus, increasing session length increases the removal of larger molecular weight solutes more so than smaller molecular weight solutes. Because the evaluation of dialysis dose over the past 10 years has focused nearly exclusively on the removal of urea, the prototypical water-soluble, uncharged, easily diffusible solute, the potential benefits of longer session length have been potentially hidden from view.

In addition to solute control, the adequacy of ultrafiltration also is affected significantly by the length and frequency of treatment. Large ultrafiltration volumes or rapid fluid removal can result in hypotension, cramping, and other adverse symptoms, which in turn may impede the achievement of ideal dry weight. Longer and/or more frequent sessions may decrease hemodynamic instability during hemodialysis, and thus attenuate volume overload and improve blood pressure control. Published studies of dialysis session length and hemodialysis outcomes are listed in Table 1.

Randomized Clinical Trials of Dialysis Session Length

To date, the NCDS remains the only randomized controlled trial evaluating the effect of dialysis session length on patient outcomes. The NCDS enrolled 165 patients into 4 treatment arms in a 2 × 2 factorial design. Patients were randomized to 1 of 2 target session lengths (4.5–5 and 2.5–3.5 h) and 1 of 2 target blood urea nitrogen concentrations (TAC_{urea} 100 mg/dL and 50 mg/dL). The TAC_{urea} achieved were 89 and 52 mg/dL, respectively (corresponding roughly to Kt/V_{urea} of 0.6 and 1.0). All patients received hemodialysis 3

times per week using cellulose dialyzers and acetate-based dialysate. A high rate of treatment failure in the high blood urea nitrogen short-time group led to discontinuation of this arm after 20 weeks; all other arms were followed-up for at least 24 weeks.

In the primary report of the first 151 patients, longer session length had no significant effect on the combined end point of death or study withdrawal, and a borderline beneficial effect on the rate of non–access-related hospitalizations ($P = .06$).[2] In a subsequent analysis,[9] the session length was unassociated with the primary end point of death or study withdrawal. However, the session length was a significant predictor of the secondary end point of death, study withdrawal, or hospitalization, even after controlling for TAC_{urea}, nutritional status, and other potential confounders. Compared with the strong effect of TAC_{urea} on morbidity and mortality, the session length was considered to have secondary, more minor effects. The investigators presciently concluded that the study conclusions should be interpreted cautiously, given the design and limited power of NCDS. In retrospect, one might argue that the NCDS' session length ($P = .06$) was the most significant (important) nonsignificant (statistically) effect in the history of dialysis research.

Observational Studies of Dialysis Session Length

Observational studies of dialysis session length have produced conflicting results, perhaps relating to one or more of the following factors. First, dialysis practices have evolved considerably over the past 2 decades. Changes in practice such as bicarbonate-based dialysate, biocompatible membranes, high-efficiency high-flux dialyzers, the introduction of erythropoietin, and routine measurement of dialysis dose occurred simultaneously with the decrease in session length, and thus may confound the analyses. Second, based on usual practice, session length is correlated or collinear with several other factors associated with outcomes, including sex, body size, nutritional status, and serum phosphorus concentration. To adequately distinguish these associations in observational data, multivariable analyses and large sample sizes are required. Third, several studies did not control for conventional measures of dialysis dose (Kt/V_{urea} or URR) and none simultaneously controlled for dose of dialysis and body size. Because time is a key component of dialysis dose, and time also is associated with body size, analyses controlling for dose of dialysis without accounting for body size may be confounded. Analyses adjusting for the clearance times time product (Kt), rather than Kt/V_{urea} or URR, may be preferred. Fourth, the range of prescribed dialysis times has narrowed considerably in the United States, which further limits statistical power. Finally, many studies analyzed prescribed, rather than delivered, time. Whether these reasons or others related to the quality of care or selection effects explain differences in US and international comparisons are unknown.

Held et al[10] investigated the relationship between session length and 3-year mortality in a sample of 600 hemodialysis patients. All patients received hemodialysis 3 times per week. At the time, no patients were dialyzed with high-flux or high-efficiency dialyzers. Patients were analyzed in 3 groups: short-time hemodialysis (3.5 h), conventional hemodialysis (3.5–4.0 h), and long-time hemodialysis (>4 h). After adjustment for demographic factors, short-time hemodialysis was associated with a significantly increased risk for mortality compared with conventional hemodialysis. The increase in risk associated with short-time hemodialysis varied with dialysis vintage, such that those receiving hemodialysis for more than 5 years had a greater than 2-fold increased risk, whereas those on dialysis for less than 1 year had a modest 17% increased risk. Whether the presence or extent of residual renal function explained the session length times vintage interaction is unknown. The risk for death was decreased by 11% in the long-time group, although this difference was not statistically significant. Interestingly, intradialytic events, including premature termination of treatment, were more frequent in the short-time dialysis group.

Using data from a national for-profit dialysis provider on 12,000 maintenance hemodialysis patients, Lowrie and Lew[11] evaluated the association of hemodialysis session length with the risk for death. In unadjusted analyses, there was a significant inverse dose-response relationship between session length and the risk for death. Patients with session lengths 2.5 hours or less had a relative risk for death of 2.35 ($P < .0001$) compared with those receiving dialysis for more than 4 hours per session. Even those with session lengths of 3.6 to 4.0 hours had a significantly increased risk for death (relative risk, 1.75; $P = .0006$). After adjusting for case-mix, the risk for death was attenuated, but remained significantly higher for those with session lengths less than 3.6 hours. After additional adjustment for laboratory variables, the predictive value of session length was extinguished.

Observational Studies Controlling for Kt/V_{urea} or URR

In contrast to these initial observational data, subsequent studies that adjusted for Kt/V_{urea} or URR generally found no independent relationship between session length and dialysis outcomes. From 1966 to 1988, Collins and Kjellstrand[12] studied 556 incident hemodialysis patients with no other comorbid illnesses. During this 22-year period, 4-year patient survival improved despite a temporal decrease in session length because per-session Kt/V_{urea} was maintained at 1.3. The investigators concluded that shortening the hemodialysis session length was not harmful if Kt/V_{urea} was maintained. Owen et al[13] evaluated the odds of death at 1 year associated with a variety of treatment-related parameters in a cohort of 13,000 hemodialysis patients. In their study, serum albumin concentration and URR were strong predictors of death. Within the range of observed session lengths (range, 3–4 h), session length was not associated significantly with the odds of death. Similar findings have been reported in other studies after controlling for Kt/V_{urea} or URR.[14,15]

In contrast, international reports have reported a positive association between session length and survival, even after accounting for Kt/V. By using data from more than 71,000 hemodialysis patients, the Japanese Society for Dialysis Therapy reported a lower risk for death associated with increases in session length up to 5.5 hours after controlling for Kt/V_{urea}.[16] In the same analyses, the risk for death associated with shorter dialysis sessions decreased with increasing dose of dialysis, up to a Kt/V of 1.8.

Several studies have noted paradoxic relations between URR or Kt/V and mortality among selected subgroups of patients, such as African Americans and women.[17,18] This phenomenon has been explained by the confounding effects of body size and nutritional status.[18] Indexing the urea product, (clearance × time) or Kt, which is associated positively with survival, to a proxy for nutritional status, V, which also is associated positively with survival, may blunt the predictive value of Kt/V (or URR). To overcome these limitations, some have proposed uncoupling Kt from V and using Kt as an index of dialysis adequacy.

In a series of analyses using a large database of hemodialysis patients, Lowrie et al[19,20] explored the relation between URR, the clearance × time product Kt, and mortality.[21] The investigators found a reverse-J or U-shaped relationship of mortality with URR, with higher mortality observed at both high and low values of URR. In contrast, Kt had a continuous monotonic relation with mortality. The risk for death decreased with progressively higher levels of Kt, independent of body size estimates.[20] Chertow et al[18] confirmed these findings in a cohort of 3,000 hemodialysis patients using for the *V* of Kt/V_{urea} the estimated total body water as determined using bioelectrical impedance analysis. Although these analyses did not separate the effects of clearance (K) from that of session length, given the standard use of high-efficiency dialyzers during the period these analyses were conducted, one might speculate that most of the variation in prescribed Kt resulted from differences in session length rather than differences in clearance. In a recent study, Port et al[22] showed that dialysis doses higher than current guidelines for dialysis adequacy (ie, a URR > 75%) were associated with a substantially lower risk for mortality among all body-size groups. An adjustment for facility-level use of high-flux dialyzers did not explain this association, hinting that session length rather than clearance may be responsible for the observed results. If these assumptions are accurate, these findings provide additional, although indirect, evidence of a benefit of increasing treatment length.

The recently completed Mortality and Morbidity in Hemodialysis (HEMO) Study was a prospective, randomized, controlled trial testing the hypotheses that higher doses of dialysis or high-flux membranes are associated with decreased morbidity and mortality.[23] The main study results indicated that neither of the interventions decreased mortality or other specified morbidities, including hospitalization, nutritional status, and quality of life. In a secondary analysis of the HEMO study, dialysis session length was not significantly associated with mortality.[24] It should be recognized, however, that dialysis doses for each patient were prescribed using the shortest session length possible. Moreover, treatments lasting more than 4.5 hours were not permitted. Thus, in effect, hemodialysis session length was not assigned randomly. Instead, session length was determined indirectly by the dose group and thereby subject to confounding by dose and bias.

Implications of Nocturnal and Short Daily Dialysis Schedules

A number of modifications to the conventional 3- to 4-hour, 3 times weekly hemodialysis schedule have evolved that have permitted investigators to explore the effects of session length and frequency outside of the usual range of prescribed treatment. These include nocturnal hemodialysis (NHD), usually 8 to 10 hours per session, 3 to 6 times per week, and short daily dialysis (SDD), commonly prescribed for 90 to 120 minutes per session, 6 to 7 times per week.

Beneficial effects on several surrogate end points have been noted with NHD and SDD. For example, both modalities have been associated with improvements in blood pressure, a decrease in antihypertensives and erythropoietin requirements, and increases in dry weight and serum albumin concentration.[25,26] In addition, NHD has been associated with increased clearance of beta-2-microglobulin, correction of hyperphosphatemia, and improvements in sleep apnea.[27-29] Regression of left ventricular hypertrophy has been noted in patients converted to SDD.[30]

Harder outcomes data for these unconventional therapies are limited. The London Daily/Nocturnal Hemodialysis study is, to date, the only published prospective (albeit nonrandomized) trial of these modalities, comparing 12 patients on NHD and 11 patients on SDD, with a control group of 20 patients on conventional hemodialysis.[31] After a mean follow-up period of 10 months (range, 5–36 mo), there were no significant differences in deaths or hospitalizations between either of the intervention groups and controls. Ting et al[32] reported a cumulative 6-year survival rate of 33%, or a crude mortality rate of approximately 11% per year, in 42 high-comorbidity patients receiving in-center SDD. Compared with the 12-month period before initiating SDD, hospitalization rates decreased 40% and hospital days decreased 34% after patients started SDD. In a pooled analysis of 72 patients receiving SDD, 2-year patient survival was 92%, corresponding to an annual mortality rate of 3.5%.[33] Similar, although more limited, data are reported for NHD. Survival rates of 87% at 5 years and 43% at 20 years have been reported from Tassin, France, for patients treated with long slow dialysis.[34] More recently, Pierratos[35] reported an annual crude mortality rate of 4.4% in 37 patients receiving home NHD after 5 years of follow-up evaluation.

Although these results generally suggest improved outcomes are possible by extending hemodialysis session length and increasing frequency, firm conclusions cannot be drawn for several reasons. First, most studies were nonrandomized, single-center case series involving small numbers of selected patients. Second, there is substantial variation in the fre-

quency of treatments across centers and among individual patients, thus there is sparse data for 3-times-per-week NHD, arguably the purest comparison group for evaluating the effects of session length against conventional dialysis schedules. Moreover, the location of treatments (home versus in-center) and other aspects of the dialysis prescription (eg, blood and dialysate flows, use of high-flux dialyzers) also confound comparisons with conventional hemodialysis.

Summary

In summary, available data support a significant positive association between hemodialysis session length and patient outcomes for conventional 3-times-per-week hemodialysis schedules. Studies suggest that within the range of treatment times prescribed in the United States (2.5–4 h), the session length has little or no significant effect on patient survival after controlling for dialysis dose by urea kinetic modeling. However, data from international end-stage renal disease programs and centers performing NHD suggest that session length (t) much longer than typically prescribed may yield additional beneficial effects on several surrogate end points, and may improve patient survival. Many questions remain unresolved, including whether the effects of session length are independent of other factors associated with dialysis adequacy (including the adequacy of ultrafiltration), and, if so, whether there are threshold effects associated with session length and mortality or morbidity. Once available, these data would assist patients and providers in dialysis decision making, particularly because longer sessions generally are undesirable. Even if mortality rates were decreased with longer session lengths, patients might elect not to increase the time beyond 3 to 4 hours for quality-of-life considerations.

In conjunction with the Centers for Medicare and Medicaid Services, the National Institutes of Health recently has sponsored 2 randomized clinical trials to examine the effects of session length and frequency on hemodialysis outcomes. One study will compare home NHD versus conventional 3-times-per-week hemodialysis, and another will compare in-center SDD versus conventional 3-times-per-week hemodialysis. Enrollment is expected to begin around May 2005. These studies should help to clarify the relationship between session length and outcomes. In the meantime, observational studies should attempt to evaluate hemodialysis session length independent of efficiency, and should consider the evaluation of dose using other clearance parameters and the adequacy of ultrafiltration in addition to urea kinetics.

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