CLINICAL STUDY

Test of the recommended dialysis dose on one-year mortality of nondiabetic maintenance hemodialysis patients; observations from a single dialysis unit

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ABSTRACT

Background: The optimal delivered dialysis dose has been of a great interest for the last three decades, though a clear cut point has not been reached yet. We aimed to evaluate the relationship between one-year mortality and the delivered dialysis dose, which was recommended by Kidney Disease Outcomes Quality Initiative (KDOQI), in our maintenance hemodialysis (MHD) patients.

Methods: This was a single center, prospective observational study with one year of follow-up. Patients with extremes of age, BMI, residual renal function, diabetes mellitus, severe infection, malignancy, and recent hospitalization within the last three months were excluded. Demographic, anthropometric, laboratory, and outcome data (mortality as the primary) were prospectively collected. Patients were classified into two groups according to baseline spKt/V levels; group 1 (n = 20): spKt/V ≤ 1.4, group 2 (n = 60): spKt/V > 1.4.

Results: Median (IQR) age and hemodialysis vintage of all patients (M/F: 41/39) were 49.5 (29) years and 60 (94) months, respectively. Both groups had similar characteristics, with the exception of significantly higher BMI (24 vs. 21.7, p = 0.012), serum creatinine and uric acids, and lower spKt/V (1.30 vs. 1.71, p < 0.001) in group 1. Overall death occurred in seven (8.75%) patients (5 from group 1 and 2 from group 2). Patients in group 1 had significantly higher one-year mortality rate and shorter survival time (25% vs. 3.3%, p = 0.003 and 43.9 vs. 47.3 weeks, p = 0.003, respectively).

Conclusions: Higher spKt/V (>1.4) was associated with a lower one-year mortality in this small cohort of patients.

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Introduction

Although maintenance hemodialysis (MHD) prevents death from uremia, mortality rates remain unacceptably high (10- to 20-fold more than the general population). Numerous risk factors that are related and unrelated to the dialysis procedure have been associated with decreased survival. Cardiovascular disease and infections are the major causes of death in this population. Additional risk factors that are associated with the hemodialysis procedure, including dialysis vintage, delivered dialysis dose, membrane biocompatibility and control of fluid balance and hypertension, have also been correlated with patient outcomes. From the beginning of the dialysis era, optimal dialysis dose and frequency have been central topics in the prescription of hemodialysis. However, an agreement for the optimum spKt/V has not been reached yet across observational and randomized studies, due to the confounding effects of the determinants of Kt/V, heterogeneity of the studied patient populations and the statistical methods that were used. As a result, in addition to under dialysis, very high Kt/V values were also associated with increased mortality. The National Kidney Foundation’s KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update recommends a target single pool Kt/V (spKt/V) of 1.4 per hemodialysis session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2. Therefore, we aimed to analyze the effect of suggested target spKt/V value (1.4) on short-term (one year) mortality in nondiabetic MHD population from a single dialysis unit.

Materials and methods

In January, 2013, a total of 80 patients with ESRD who were on MHD for at least three months were included
in this prospective study. Patients with a history of hospitalization, major surgery, obvious infections, inflammatory disease within the preceding three months, end-stage liver disease, metastatic malignancies, and malabsorption syndromes were excluded. We studied only non-diabetic and anuric (<100 mL/day) patients to minimize the confounding effects of diabetes mellitus and residual renal function on patient survival. The study population was followed up prospectively for 12 months and the primary outcome was mortality.

All patients had received conventional HD thrice a week with standard bicarbonate and 140 mEq/L sodium containing dialysate bath using low-flux biocompatible HD membranes. The blood flow rates ranged between 300 and 350 mL/min and the dialysate flow rate was kept constant at 500 mL/min. None of the patients reused the dialyzer, and neither bacteria nor pyrogen was grown in the dialysate prepared from water generated by reverse osmosis. Patients were not allowed to have snacks during dialysis. Postdialysis blood urea levels of the same dialysis session were measured to calculate the delivered dose of dialysis by using the second-generation Ln formula \( Kt/V = -\ln \left( R - 0.008 \times t \right) + (4-3.5 \times R) \times UF/W \), \( R \): [predialysis blood urea nitrogen (BUN)—postdialysis BUN/predialysis BUN], \( t \): time (hour), UF: actual ultrafiltration, \( W \): postdialysis bodyweight) which was asserted by Daugirdas. The average of \( spKt/V \) for January and February 2013 was used for analysis. Using the National Kidney Foundation’s KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update, patients were classified into two groups according to recommended target of single-pool \( Kt/V \) (\( spKt/V \)) levels per hemodialysis session for patients treated thrice weekly; group 1 \((n = 20)\): \( spKt/V \leq 1.4 \), group 2 \((n = 60)\): \( spKt/V > 1.4 \).

Initial assessment including demographic, anthropometric and biochemical data was made for all patients in January 2013. Body weight and height were measured 15–30 minutes after the end of mid-week HD sessions, and body mass index (BMI) was calculated as body weight divided by height squared (kg/m\(^2\)) for each case.

For each patient, predialysis systolic and diastolic blood pressures were recorded during the 12 successive dialysis sessions. Interdialytic weight gain (IDWG) was expressed as the difference between the predialysis weight and the weight at the end of the previous HD session. With regard to IDWG, the average of 12 sessions within four weeks before enrollment was used for the analyses. Relative interdialytic weight gain (RIDWG) was calculated as the average of IDWG divided by the respective dry weight.

Venous blood samples were drawn from all the subjects after an overnight fasting period before the mid-week session. All biochemical analyses, including serum urea, creatinine, albumin, total cholesterol, triglyceride, low-density lipoprotein (LDL), calcium, phosphorus, intact parathormone (PTH), bicarbonate, total iron-binding capacity (TIBC), and ferritin, were performed by automated procedures. High-sensitive C-reactive protein (hs-CRP) levels were measured by using nephelometric method (Catalog No: 11355279 216, Roche, Hitachi Cobas C system, Mannheim, Germany).

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study that was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and approved by the institutional ethics committee.

**Statistical analysis**

SPSS 20.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis. Skewed data were presented as median and interquartile range (IQR). Yates correction \( \chi^2 \)-test was used for the comparison of nonparametric variables. Mann–Whitney \( U \)-test was used for the comparison of parametric variables between groups. Spearman’s test was used for correlation analysis. ROC curve analyze used for estimating sensitivity-specificity and optimal cutoff value of \( spKt/V \) for predicting death. Multivariate Cox proportional hazard model (Enter method) analysis was performed to determine independent risk factors for patient mortality. Adjustments were made for BMI and serum albumin by linear regression model to identify the independent relationship between \( spKt/V \) and death. Survival was estimated by the Kaplan–Meier and log-rank tests. \( p \) Values <0.05 was considered significant.

**Results**

Median (IQR) age and HD vintage of all patients (M/F: 41/39) were 49.5 (29) years and 60 (94) months, respectively. Median (IQR) \( spKt/V \) of all patients was 1.60 (0.39). All patients had AV fistula, except for six with tunneled central venous catheters and two with AV grafts (there were no differences between the groups). Overall seven patients died during the one-year observational period. Of seven patients who died, causes of death were as follows: three (42.8%) ischemic heart disease, two (28.6%) infection, one (14.3%) complications of HD insufficiency, such as uremia, hyperkalemia, and hypervolemia, and one (14.3%) unidentified cause. When compared to group 1, group 2 patients had significantly lower dry weight (64.2 (27) vs. 55.5 (15), \( p \): 0.003, respectively), lower BMI (24.1 (8) vs. 21.7 (5), \( p \): 0.012, respectively),
lower serum creatinine (10.5 (3.8) vs. 8.6 (2.6), p = 0.009, respectively), lower uric acid (6.6 (1.9) vs. 5.8 (1.4), p = 0.002, respectively) and higher spKt/V (1.30 (0.19) vs. 1.71 (0.35), p < 0.001, respectively) levels. There were no significant differences between the two groups regarding age, gender, HD vintage, systolic and diastolic blood pressures, RIDWG (%), predialysis serum levels of urea, hemoglobin, sodium, potassium, calcium, phosphorus, CaXp product, intact PTH, albumin, TIBC, ferritin, total cholesterol, LDL, triglyceride, bicarbonate, and hs-CRP (Table 1).

In correlation analysis (Table 2), statistically significantly negative correlations were found between spKt/V and age (r = −0.260, p = 0.020), male gender (r = −0.338, p = 0.002), dry weight (r = −0.435, p < 0.001), BMI (r = −0.256, p = 0.022), serum urea (r = −0.271, p = 0.015), creatinine (r = −0.330, p = 0.003), uric acid (r = −0.334, p = 0.002) levels, and death (r = −0.347, p = 0.002). However, HD vintage, RIDWG, systolic and diastolic blood pressure, serum sodium, potassium, hemoglobin, calcium, phosphorus, intact PTH, albumin, ferritin, total cholesterol, triglyceride, LDL, hs-CRP levels were not correlated with spKt/V.

Figure 1 illustrates ROC curve analysis of the relationship between spKt/V and mortality. We found that the optimal cutoff value of spKt/V for predicting death was 1.390 (p = 0.002, area under the curve: 0.854, standard error: 0.081, 95% confidence interval (CI): 0.695–1.000). The sensitivity and specificity of this cutoff value were 71.4% and 83.6%, respectively.

Table 3 shows one-year survival analysis according to the spKt/V groups. Out of 80 patients, seven patients died during the one-year observational period. Mortality rate and survival time of all patients were 8.7% (7/80) and 46.4 ± 0.75 weeks, respectively. Mortality rate was significantly higher in group 1 patients compared to group 2 patients. The bold and italic font are used to point out the statistically significant variables.

### Table 1. Characteristics of all patients and groups (Mann–Whitney U-test).

|                           | All patients (n = 80) | Group 1 (n = 20) | Group 2 (n = 60) | p     |
|---------------------------|-----------------------|------------------|------------------|-------|
| **Demographics**          |                       |                  |                  |       |
| Age (y)                   | 49.5 (29)             | 52.5 (26)        | 46.5 (30)        | 0.107 |
| Sex (male/female)         | 41/39                 | 13/7             | 28/32            | 0.200 |
| Duration on HD (months)   | 60 (94)               | 64 (113)         | 60 (82)          | 0.846 |
| Dry weight (kg)           | 56.7 (18)             | 64.2 (27)        | 55.5 (15)        | 0.003 |
| Body mass index (kg/m²)   | 22.6 (6)              | 24.1 (8)         | 21.7 (5)         | 0.012 |
| Systolic BP (mm Hg)       | 110 (20)              | 110 (28)         | 112.5 (30)       | 0.469 |
| Diastolic BP (mm Hg)      | 72.5 (20)             | 70 (20)          | 77.5 (20)        | 0.823 |
| RIDWG (%)                 | 4.6 (2.1)             | 4.6 (2.1)        | 4.7 (2.0)        | 0.120 |
| **Laboratory**            |                       |                  |                  |       |
| Urea (mg/dL)              | 131 (75)              | 146.5 (101)      | 122.1 (66)       | 0.104 |
| Creatinine (mg/dL)        | 8.7 (2.8)             | 10.5 (3.8)       | 8.6 (2.6)        | 0.009 |
| Uric acid (mmol/L)        | 6.1 (1.6)             | 6.6 (1.9)        | 5.8 (1.4)        | 0.002 |
| Sodium (mmol/L)           | 139 (3)               | 138.5 (3)        | 139 (3)          | 0.996 |
| Potassium (meq/L)         | 5 (1.1)               | 5.1 (1.3)        | 4.9 (1.1)        | 0.850 |
| Hemoglobin (g/dl)         | 10.3 (2.1)            | 10.8 (1.7)       | 10.2 (2.3)       | 0.621 |
| Calcium (mg/dL)           | 8.7 (0.9)             | 8.5 (1.2)        | 8.8 (0.8)        | 0.684 |
| Phosphorus (mg/dL)        | 5.4 (2)               | 5.4 (2)          | 5.3 (2)          | 0.925 |
| CaXp                      | 48.2 (19)             | 49 (23)          | 48.2 (19)        | 0.938 |
| Intact PTH (pg/ml)        | 355 (552)             | 416 (739)        | 344.5 (492)      | 0.383 |
| Albumin (g/L)             | 3.9 (0.4)             | 3.8 (0.4)        | 3.9 (0.4)        | 0.951 |
| TIBC (g/L)                | 207.5 (53)            | 233 (64)         | 203 (55)         | 0.008 |
| Ferritin (ng/mL)          | 620 (562)             | 699 (892)        | 672 (533)        | 0.186 |
| Total cholesterol (mmol/L)| 166.5 (55)            | 168 (53)         | 164 (58)         | 0.881 |
| LDL (mmol/L)              | 94.5 (46)             | 93 (45)          | 94.5 (44)        | 0.590 |
| Triglyceride (mmol/L)     | 131 (75)              | 179 (103)        | 131 (79)         | 0.104 |
| Bicarbonate (meq/L)       | 22.1 (3.0)            | 21.3 (1.7)       | 22.5 (3.1)       | 0.084 |
| Hs-CRP (mg/L)             | 7.1 (17.5)            | 10.9 (10.4)      | 5.5 (24.5)       | 0.186 |

Data were presented as median (IQR). HD: Hemodialysis; DM: Diabetes mellitus; BP: Blood pressure; RIDWG: Relative interdialytic weight gain; PTH: Parathormone; TIBC: Total iron-binding capacity; LDL: Low-density lipoprotein; Hs-CRP: High-sensitive C-reactive protein.
group 2 (25% (5/20) vs. 3.3% (2/60), respectively, \( p = 0.003 \)). Compared to group 2, survival time of group 1 patients was found significantly lower (47.3 ± 0.55 weeks vs. 43.9 ± 2.41 weeks, respectively, \( p \) (Log rank): 0.003). Figure 2 illustrates the Kaplan–Meier survival analysis according to the spKt/V groups.

Advanced age (\( p: 0.025 \)) and low spKt/V (\( p: 0.005 \)) were found predictors of mortality in multivariate Cox proportional hazard model (Enter method) (Table 4). Advanced age (\( p = 0.030 \)) and low spKt/V levels (\( p = 0.014 \)) remained significantly correlated with death in linear regression analyzes even after adjustments were made for BMI and serum albumin (Table 5).

### Discussion

The patients included in this study had overall favorable baseline characteristics, which helped the elimination of some important confounders for mortality, and as a result, the overall mortality rate at one year was lower (8.75%) than the expected. Demographic and laboratory parameters were similar in patients with low and high spKt/V, except for higher BMI, creatinine and uric acid in patients with low spKt/V. In this small cohort, we found that one-year mortality was better in patients with spKt/V greater than the recommended target of 1.4. There are a number of other observational studies that have reported an improved survival with increasing the delivered dialysis dose. However, the baseline characteristics of patients, study designs, and statistical methods that were used have led to an ambiguity in identifying an optimal target of spKt/V. In addition, the relationship between \( Kt/V \) and mortality does not seem straightforward. The HEMO study, a randomized controlled trial (RCT), and the subsequent reanalysis of the same data require a particular attention at this point. The mortality outcome was investigated using

| MIS score | n | Death (n) | Survival Time (weeks) | % 95 CI | p (Log Rank) |
|-----------|---|-----------|-----------------------|---------|-------------|
| Group 1   | 20 | 5         | 43.9 ± 2.41           | 39.223  | 48.667      | 0.003 |
| Group 2   | 60 | 2         | 47.3 ± 0.55           | 46.219  | 48.381      |
| Overall   | 80 | 7         | 46.4 ± 0.755          | 44.983  | 47.942      |

### Table 3

One-year-survival analysis according to the spKt/V groups.

### Table 4

Multivariate cox proportional hazard model for patient survival.

| Predictors of mortality | \( p \) | Odds Ratio | Lower 95% CI | Upper 95% CI |
|-------------------------|--------|------------|--------------|--------------|
| Age                     | 0.025  | 1.069      | 1.008        | 1.134        |
| spKt/V                  | 0.005  | 0.013      | 0.001        | 0.274        |

### Table 5

Linear regression analysis of spKt/V as a predictor of death.

| Predictor       | Beta   | \( p \) | Lower 95% CI | Upper 95% CI |
|-----------------|--------|--------|--------------|--------------|
| Age             | 0.253  | 0.030  | -0.400       | 1.095        |
| spKt/V          | -0.286 | 0.014  | -0.455       | -0.050       |
| BMI             | -0.005 | 0.966  | -0.014       | 0.003        |
| Serum albumin   | -0.021 | 0.852  | -0.166       | 0.137        |
the intention-to-treat analysis in the original HEMO study, and there were no statistically significant difference between low and high dialysis doses for a mean difference in $eKt/V$ ($spKt/V – 0.6Kt/V + 0.03$) of 0.37.\textsuperscript{11} When as-treated analysis was done; however, the one-year mortality rate was found significantly higher in patients with lower $eKt/V$ as compared to the reference of 1.35–1.45 $eKt/V$ units.\textsuperscript{12} An additional detail from the second analysis of the HEMO cohort was that, although patients with the lowest quintile of achieved $eKt/V$ in the high-dose group had an average $eKt/V$ greater than the entire standard dose group; their mortality rate was still 59% higher. These findings suggest that the association between increased mortality and low $eKt/V$ may not be explained solely by $Kt/V$ itself. In a closer look, achieving a target level of $Kt/V$ requires the contribution of its determinants, which are $V$ for the volume of distribution (total body water), $t$ for dialysis time and $K$ for clearance per unit of time (determined by blood flow rate, dialyzer and dialysate flow rate). All of these factors by themselves have also been associated with mortality in hemodialysis.\textsuperscript{13–15} With these parameters in hand, one can predict that a high $Kt/V$ can easily be obtained in small-sized (malnourished) patients, whereas relatively lower $Kt/V$ is more likely in large-sized (high BMI) patients, and as a consequence, the survivals of these patients would be found disproportionate to their $Kt/V$ values. With reference to the aforementioned determinants of $Kt/V$, patients with the lowest $eKt/V$ quintile from the high-dose group (in the HEMO cohort) were more likely to have inadequacy of $K$ and/or $t$ for some reasons such as black race, baseline Karnofsky score, and vascular access type. On the other hand, very high levels of $Kt/V$ were also associated with an increased mortality.\textsuperscript{16,17} This twisted association is mostly explained by the fact that excessive $Kt/V$ values are more likely to be associated with protein energy wasting. It is, therefore, important to try to analyze patients stratified according to similar baseline characteristics that are known to have a bidirectional effects on both survival and achieved $Kt/V$.

Another important issue in evaluating the relationship between $spKt/V$ and mortality is that the determinants of $Kt/V$ have effects on outcomes before the initial evaluation and they can also change throughout the study period from the initial sampling time till the end. This reduces the predictability of initial $Kt/V$ sampling, such as the baseline $eKt/V$ was predictive of mortality for no more than one year in the reanalysis of the HEMO study.\textsuperscript{12} The variables related to mortality and $Kt/V$ that can change over time are collectively called time-varying confounders, and it is claimed that they may not be sufficiently controlled in longitudinal studies with the conventional Cox regression models.\textsuperscript{18} In a recent report with a large cohort of MHD patients, Lertdumrongluk et al. used a marginal structural model analysis model to overcome the time-varying confounders influence, and they found that there was a robust inverse relationship between mortality and $spKt/V$ up until $1.8 \leq 2.0$ units of $spKt/V$, above which the mortality benefit showed a plateau.\textsuperscript{18} Furthermore, the mortality benefit of higher $spKt/V$ was consistent across stratifications for confounders, such as sex, ethnicity, age, diabetes status, albumin levels, BMI, and dialysis vintage.\textsuperscript{18}

**Conclusions**

Consistent with other large observational studies and one RCT, higher baseline $spKt/V$ was associated with lower one-year mortality in this small, homogeneous cohort of patients. The study design, statistical methods, and stratification of patients according to confounders appear to influence the consistency of results between studies.

**Disclosure statement**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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