

Impact of hemodialysis dose and frequency on survival of patients on chronic hemodialysis in Lithuania during 1998–2005

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Key words: hemodialysis; Kt/V; survival.

Summary. *Introduction.* The question of the targets of dialysis dosing remains controversial since the beginning of the long-term dialysis treatment era. It is still uncertain if higher dialysis dose is better.

The aim of our study was to investigate issues of dialysis dose in Lithuania during the period of 1998–2005 and to determine associations between hemodialysis dose and survival of patients on chronic hemodialysis.

Material and methods. We analyzed data of all patients who started hemodialysis due to end-stage renal disease in Lithuania between January 1, 1998, and December 31, 2005. The information about hemodialysis frequency, duration, and adequacy (according to Kt/V) was obtained from medical documentation. The overall survival rate was estimated using the Kaplan-Meier method. Survival comparisons were made using the log-rank or Breslow tests. Univariate Cox proportional hazards analysis was used to select variables significantly associated with the risk of death; then these variables were included in multivariate Cox proportional hazards models.

Results. During the study period, from 2428 patients who started chronic hemodialysis, 58.5% of patients started hemodialysis three times a week. More than one-third (36.2%) of patients were dialyzed twice weekly, and 5.3% of patients started hemodialysis once weekly. Survival analysis revealed that patients dialyzed less than three times per week survived shorter than patients receiving a higher dialysis dose. Duration of HD session of ≤ 8 hours per week was an independent risk factor for mortality. A higher mean Kt/V was associated with better survival of patients on chronic hemodialysis.

Conclusions. Dialysis frequency and weekly duration of HD sessions were dependent on HD accessibility in Lithuania during the period of 1998–2005. Better survival of patients on chronic hemodialysis was associated with a higher hemodialysis dose.

Introduction

The issue of optimal dialysis dose has been hot and controversial since the beginning of the long-term dialysis treatment era. Observational studies suggested a continuous benefit from increasing the delivered dialysis dose well above the minimal targets recommended by the international guidelines (1–3), but the randomized controlled trials HEMO and ADEMEX concluded that there were no benefits to patients' outcome from higher dialysis doses than those recommended by the present guidelines (4, 5).

Debate continues about the optimal number and length of hemodialysis (HD) sessions (6). Three HD sessions a week are most common. Earlier reports showed that twice-weekly schedules are sometimes

used for elderly patients, women, patients with low body mass index, and patients with renal residual function at the beginning of renal replacement therapy (RRT) (7), but they are not recommended by the current international guidelines or in patients with urea clearance of < 2 mL/min (8).

Traditionally, dialysis adequacy has been quantified referring to the kinetics of urea. An index of dialysis dose is the fractional clearance of urea, which is commonly expressed as Kt/V. Kt/V is defined as the dialyzer clearance of urea (K, obtained from the manufacturer in mL/min, and periodically measured and verified by the dialysis team) multiplied by the duration of the dialysis treatment (t, in minutes) divided by the volume of distribution of urea in the

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body (V, in mL), which is approximately equal to the total body water. There is no universally accepted target value for the Kt/V. The National Cooperative Dialysis Study (NCDS) found that a Kt/V urea above 0.9 with thrice-weekly treatment provided an “adequate” dialysis prescription (9). A Kt/V value of 1.0 was widely accepted as representing adequate dialysis. Shorter dialysis times were permitted as long as the goal Kt/V was attained. Therefore, the characteristics of the dialysis population have changed dramatically compared with the NCDS dialysis population, with a sharp increase in the proportion of elderly patients and diabetic patients, and the radical changes in the HD technology have occurred. After high-efficiency HD became widely used, it became manifest that urea follows a double-pool kinetics, rather than the single-pool one. Urea rebound at the end of HD sessions was reported. Therefore, not all investigators accept the Kt/V as the optimal method for assessing the adequacy of hemodialysis. From all methods used to measure dialysis adequacy, the current international guidelines give preference to Kt/V as the best outcome correlate because of its simplicity and accuracy. The 2006 K/DOQI guidelines for hemodialysis patients with minimal residual renal function (less than 2 mL/min per 1.73 m²) recommend that a single-pool Kt/V of 1.2 (or a urea reduction rate of 65%) should be a minimally adequate dose and a single-pool Kt/V of 1.4 (or a urea reduction rate of 70%) should be a target recommended dose (8). The European Best Practice Guidelines recommend higher values: double-pool Kt/V_{urea} of at least 1.2 and single-pool Kt/V_{urea} of at least 1.4 (10). Recent studies have demonstrated a great international variability in weekly HD duration and some discrepancies between current practices and recommendations of international guidelines (11, 12). The aim of our study was to investigate the issues of dialysis dose in Lithuania during the period of 1998–2005 and to determine associations between hemodialysis dose and survival of patients on chronic hemodialysis.

Material and methods

All patients who started chronic HD due to ESRD in Lithuania between January 1, 1998, and December 31, 2005, were enrolled into this study.

Because there is no official renal registry in Lithuania, in December of each year, all HD centers of Lithuania were visited by workers of the Department of Nephrology of the Hospital of Kaunas University of Medicine, and data on all HD patients were collected, using special paper questionnaires. Using

data, collected at annual visits to HD centers, demographic data, cause of ESRD, date of HD start and how it was started, the duration of HD (hours per week), number of HD sessions per week, last measured HD quality index (single-pool Kt/V), and outcome were recorded for every patient in a special form. For patients who were dialyzed more than one year, parameters of HD dose were recorded more than one time; therefore, we estimated their mean values.

The statistical analysis was performed using the SPSS program (version 15.0, SPSS Inc. Chicago, IL, USA). Categorical variables were described as frequencies and continuous variables as means with their ranges. Distribution of data for normality was tested using the Kolmogorov-Smirnov test (Lilliefors modification). Differences between groups of normally distributed data were tested using the Student's *t* test for continuous variables, chi-square test for discrete variables, and ANOVA test for more than two groups. Differences between groups of skewed data were compared using nonparametric methods: the Mann-Whitney *U* test for two groups and the Kruskal-Wallis *H* test for more than two groups. For analysis of outcomes, the cumulative survival rate was estimated using the Kaplan-Meier method. The event of interest was death. Patients were censored at the time of transplantation or transfer to PD, at loss to follow-up, and at the end of the study. Survival comparisons were made using the log-rank or Breslow tests. Univariate Cox proportional hazards analysis was used to select variables significantly associated with the risk of death; then these variables were included in multivariate Cox proportional hazards models. Differences were considered significant at $P < 0.05$.

Results

At the time of review, information in the records about frequency and duration of HD procedure was available for 2063 patients (85%) out of 2428 patients who started chronic HD during the mentioned period. More than half (58.5%) of patients started HD thrice weekly. More than one-third (36.2%) of patients were dialyzed twice weekly, and 5.3% of patients started HD once weekly. Significant changes in HD prescription during study period were observed: the proportion of patients who started HD thrice weekly increased from 45.9% in 1998 to 68.1% in 2005 and the proportion of patients who started HD twice weekly and once weekly decreased from 42.4% in 1998 to 29.6% in 2005 and from 10.7% in 1998 to 2.3% in 2005, respectively (Fig. 1).

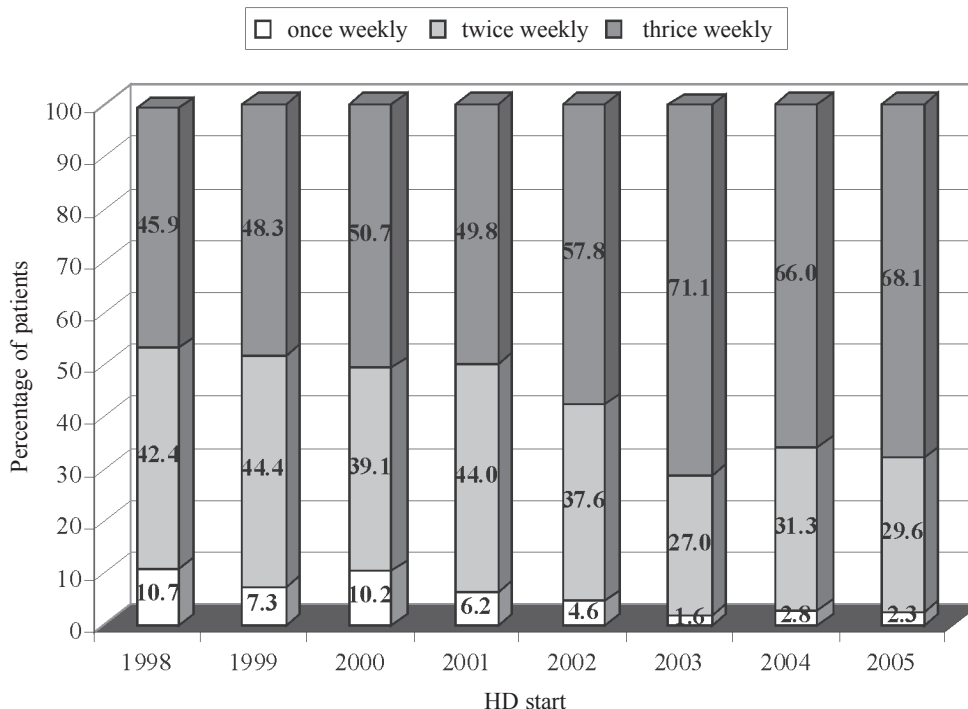


Fig. 1. Hemodialysis frequency in Lithuania during the period of 1998–2005

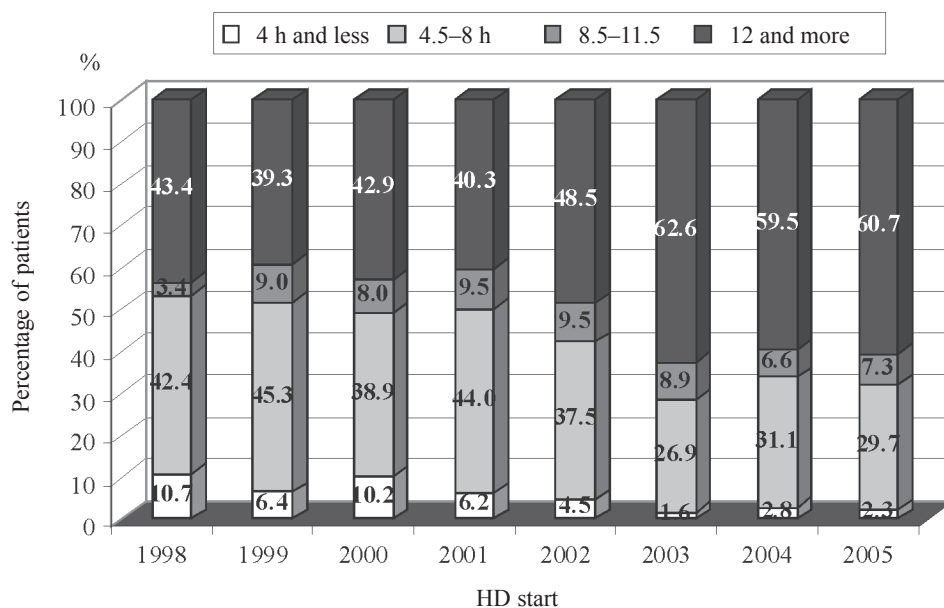


Fig. 2. Weekly duration of hemodialysis sessions in Lithuania starting hemodialysis treatment in 1998–2005

Patients who had three sessions a week were more likely to be younger (mean age, 53.11 ± 16.29 years vs. 63.09 ± 12.17 years; $P < 0.001$) and males (56.2% versus 39.4%, $P < 0.001$) than those who started HD one time per week.

Univariate Cox proportional hazards analysis revealed that the relative risk of death increased to 2.175 (95% CI, 1.87–2.53; $P < 0.001$) if the mean number of HD sessions per week was less than three. After adjustment for age, sex, and primary kidney disease,

the mean number of HD sessions less than 3 times per week remained an independent risk factor for death (RR, 1.92; 95% CI, 1.643–2.24; $P < 0.001$).

During study period, we observed prolongation of weekly HD time. In 1998, only 43.4% of patients were dialyzed 12 hours or more per week. At the end of study, 60.7% of patients had such a schedule. The proportion of patients receiving HD treatment of 4 hours and less per week decreased from 10.7% in 1998 to 2.3% in 2005 (Fig. 2).

The duration of HD session of ≤ 8 hours per week was an independent risk factor for higher mortality (Table 1).

We failed to demonstrate any survival advantage in patients who were dialyzed ≥ 12 hours per week except in those who started HD treatment in the period of 2002–2003 and women on dialysis for ≥ 30 months.

During the study period, the mean Kt/V was 1.177 ± 0.239 . A higher Kt/V index was seen in women and younger patients. It was dependent on the duration of HD treatment: Kt/V was the smallest (1.16) in the first year on HD and the greatest (1.37) in the seventh year of HD ($P < 0.001$). Our data suggested that a higher Kt/V was beneficial. Even after adjustment for age and sex, a significant decrease in the probability of death was seen in all Kt/V categories above 1.0 (Table 2).

Because associations between Kt/V and survival of patients may be affected by differences in residual renal function, the analysis of patients on RRT for > 2 years was performed separately. Kaplan-Meier analysis revealed improved survival of patients with a mean Kt/V of ≥ 1.2 (Fig. 3).

We noticed that after adjustment for age, sex, and primary kidney disease survival advantage for higher Kt/V disappeared. Because recent studies reported remaining of residual renal function up to 5 years, we repeated survival analysis of patients who received RRT for more than 5 years. Results showed that the mean Kt/V of ≥ 1.2 was associated with a higher survival rate only in women (Breslow test, $P = 0.034$).

Discussions

Associations between dialysis dose and adequacy, and patients' outcomes have been studied for the first time in Lithuania. Our results suggested that a higher dialysis dose was associated with improved survival.

Nephrologists treating patients on chronic HD are trying to search for the best, or in other words, "adequate" dialysis treatment to improve survival and quality of life as much as possible. Assessment of adequacy of dialysis is a very important issue in the management of patients on chronic hemodialysis. Simply monitoring of laboratory parameters (blood urea or creatinine concentration) is insufficient because low concentrations of urea or creatinine can reflect

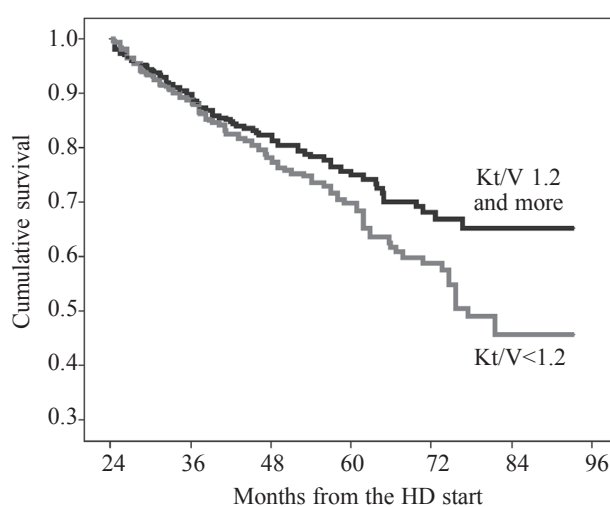


Fig. 3. Survival of patients on chronic hemodialysis more than 24 months according to Kt/V index

Table 1. Effect of HD duration of ≤ 8 hours per week on relative mortality risk, adjusted for age, sex, and prevalence of diabetes

Factor	Relative risk	P	95% CI	
			Lower limit	Upper limit
HD duration of ≤ 8 hours per week	1.983	<0.001	1.639	2.400
Age	1.025	<0.001	1.018	1.032
Sex	0.899	0.235	0.755	1.071
Diabetes mellitus	2.268	<0.001	1.861	2.765

Table 2. Effect of Kt/V on relative mortality risk, adjusted for age and sex

Factor	Relative risk	P	95% CI	
			Lower limit	Upper limit
Mean Kt/V <math>< 1.0</math>	1.0			
Kt/V 1.0–1.19	0.622	<0.001	0.478	0.807
Kt/V 1.2–1.39	0.517	<0.001	0.387	0.690
Kt/V ≥ 1.4	0.713	0.037	0.518	0.980
Age	1.031	<0.001	1.023	1.039
Sex (female=1)	1.030	0.775	0.841	1.260

inadequate nutrition or mobility. Monitoring uremic symptoms alone is also insufficient because these symptoms can be eliminated by improved anemia management with erythropoiesis-stimulating agents. Charra et al. suggest that patient survival should be considered as the best overall index of adequacy of dialysis (13). They reported one of the best dialysis survival estimates of any program or registry, with a 15-year survival rate of 65% in 445 patients followed up from 1970 to 1990. Those patients who were dialyzed very intensively (Kt/V of 1.67) also had a high incidence of full rehabilitation and almost all patients were normotensive without antihypertensive medications (13). The comparison of patient survival among different countries or units is complicated due to a large number of factors, which were not related to treatment. Mortality rates for age-, race-, and primary kidney disease-adjusted groups of patients observed in Tassin were 2- to 3-fold lower than those for the corresponding patients in the United States, and this could be probably explained by the larger dialysis dose used (14). Studies both in Germany and the United States have documented associations between shorter dialysis time and poorer outcome (15, 16). Patients dialyzed less than 3.5 hours 3 times per week had an approximately 2-fold greater risk of mortality compared to patients dialyzed 4 or more hours 3 times per week (15).

Our data suggested that duration of HD session of ≤ 8 hours per week was an independent risk factor for mortality, but we failed to prove any survival advantage in patients who were dialyzed ≥ 12 hours per week except in those who started HD treatment in the period of 2002–2003 and women on dialysis for ≥ 30 months. In addition, we found that the mean Kt/V of ≥ 1.2 was associated with a higher survival rate only in women (Breslow test, $P=0.034$). It shows that a higher dialysis dose is beneficial for women. Similar findings were reported in the HEMO study: subgroup analysis revealed a significant survival benefit for

women receiving a high dialysis dose (19 percent lower risk of death than women in the standard dose group) (17).

Great differences in the number and length of HD sessions have been reported across different countries and patients' subgroups. The proportion of patients receiving HD sessions of <12 h varies from 3% to 51% among countries. Twice-weekly schedules are generally not recommended, and indeed only 4% of patients in Europe have such a schedule, to which should be added the 0.4% with only one session (12). Despite the fact that thrice-weekly hemodialysis is regarded as the standard for maintenance dialysis, the prescription of twice-weekly hemodialysis with a longer treatment time is common in poorer countries, such as Hong Kong and others, to allow more patients with renal failure to receive treatment (18). Dialysis frequency and weekly duration time in Lithuania at the beginning of study period also reflected HD accessibility. Insufficient HD network was the main reason for starting dialysis treatment less than three times per week. Over the period of 1998–2005, the HD services significantly expanded in Lithuania. Therefore, significant changes in HD prescription at the end of study period were observed: the proportion of patients who started HD thrice weekly significantly increased and the proportion of patients who started HD twice weekly or once weekly – decreased. However, the survival of patients who were dialyzed less than three times per week was worse compared with those patients who were dialyzed three or more times per week. These findings suggest that the quality of HD can be improved by increasing its frequency.

Conclusions

1. Dialysis frequency and weekly duration time was dependent on hemodialysis accessibility in Lithuania during the period of 1998–2005.
2. Higher dialysis dose was associated with better survival of patients on chronic hemodialysis in Lithuania.

Hemodializės dozės ir dažnio reikšmė pacientų, sergančių galutiniu inkstų nepakankamumu bei gydomų hemodializėmis, išgyvenimui Lietuvoje 1998–2005 m.

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Raktažodžiai: hemodializė, Kt/V, išgyvenimas.

Santrauka. *Įvadas.* Dėl dializės dozavimo diskutuojama nuo pat šio gydymo metodo atsiradimo. Iki šiol nepakankamai ištirta, ar didesnė dializės dozė yra geriau.

Tyrimo tikslas. Ištirti dializės dozavimo savitumus Lietuvoje 1998–2005 m. ir nustatyti hemodializė dozę bei hemodializėmis gydomų pacientų išgyvenimo sąsajas.

Tyrimo medžiaga bei metodai. Išnagrinėjome duomenis visų pacientų, kurie dėl galutinio inkstų nepakankamumo pradėjo gydymą hemodializėmis Lietuvoje nuo 1998 m. sausio 1 d. iki 2005 m. gruodžio 31 d. Informacija apie hemodializė dažnį, trukmę ir adekvatumą (pagal Kt/V žymenį) surinkta iš medicinos dokumentacijos. Išgyvenimui nustatyti naudotas Kaplano ir Mejerio metodas. Ligonų išgyvenimui palyginti naudoti log-rank arba Breslovo testai. Vienmatės Cox regresijos metodas padėjo atrinkti kintamuosius, reikšmingai susijusius su mirtingumo rizika, kuriuos vėliau įtraukėme į daugiamatės Cox regresijos modelius. Duomenų skirtumai tarp grupių statistiškai reikšmingi, kai $p < 0,05$.

Rezultatai. Tiriamuoju laikotarpiu iš 2428 pacientų 58,5 proc. gydymas hemodializėmis pradėtas tris kartus per savaitę; 36,2 proc. pacientų buvo dializuoti du kartus per savaitę, 5,3 proc. pacientų gydymas hemodialize pradėtas vieną kartą per savaitę. Išgyvenimo analizė parodė, kad pacientai, kurie bet kuriuo laikotarpiu buvo dializuoti mažiau nei tris kartus per savaitę, išgyveno trumpiau nei tie, kurių hemodializė doze buvo didesnė. Hemodializės procedūros trukmė ≤ 8 val. per savaitę buvo nepriklausomas mirtingumo rizikos veiksnys. Didesnis vidutinis Kt/V žymuo buvo susijęs su geresniu hemodializėmis gydomų pacientų išgyvenimu.

Išvados. Dializė dažnis ir savaitinė trukmė Lietuvoje 1998–2005 m. priklausė nuo hemodializė prieinamumo. Geresnis pacientų, gydomų hemodializėmis, išgyvenimas buvo susijęs su didesne hemodializė doze.

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