Length of Dialysis Session Is More Important Than Large Kt/V in Hemodialysis

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Long, slow hemodialysis (3 × 8 hours/week) has been used without significant modification in Tassin, France, for 30 years with excellent morbidity and mortality rates. A long dialysis session easily provides high Kt/V_{urea} and allows for good control of nutrition and correction of anemia with a limited need for erythropoietin (EPO). Control of serum phosphate and potassium is usually achieved with low-dose medication. The good survival achieved by long hemodialysis sessions is essentially due to lower cardiovascular morbidity and mortality than in short dialysis sessions. This, in turn, is mainly explained by good blood pressure (BP) control without the need for antihypertensive medication. Normotension in this setting is due to the gentle but powerful ultrafiltration provided by the long sessions, associated with a low salt diet and moderate interdialytic weight gains. These allow for adequate control of extracellular volume (dry weight) in most patients without important intradialytic morbidity. Therefore, increasing the length of the dialysis session seems to be the best way of achieving satisfactory long-term clinical results.

(Home Hemodial Int, Vol. 3, 16–22, 1999)

Key words

Hemodialysis dose duration, Kt/V, blood pressure, mortality, albumin, middle molecules, ultrafiltration

Introduction

After maintenance dialysis was shown to be feasible in 1960 [1], the process of trial and error over the following decade led to the following definition of adequate hemodialysis (HD): three 8 – 12 hour dialysis sessions per week [2]. After this initial era of empirical development, technical advances, changing scientific views on uremia pathophysiology [3], as well as social and economical pressure led to the acceptance of shortened dialysis treatments. This shortened HD was understandably welcomed by most patients and treatment teams and rapidly became the universal HD treatment. The traditional HD with long treatment sessions disappeared, except in a few units, where it was used for overnight and at-home treatments in particular. In Tassin, France, the 8-hour dialysis dose remained the standard treatment method [4,5].

After the National Cooperative Dialysis Study (NCDS) report [6], urea removal appeared to be the best way of measuring the dose of treatment. Gotch and Sargent developed the Kt/V_{urea} concept [7], and later their mechanistic analysis of the NCDS data [8] led to the view that the HD session time could be reduced, ultimately aiming at a "minimal dialysis dose" [9]. The 1989 Dallas meeting came as the breaking point in this evolution [10]. Since then, the prescribed and delivered doses of dialysis have been increasing and mortality has been decreasing [11]. The respective benefits derived from increasing the dose [12–16] and the time [17–20] have been actively discussed. In light of the long-term Tassin experience we present our view that in terms of clinical outcome, the length of the dialysis session may be more important than Kt/V_{urea}.

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Patients and methods

For 30 years the method of dialysis used in Tassin has remained unchanged. Three 8-hour sessions are performed each week (overnight or in the daytime, according to patient resources and preferences), using a cellulosic membrane, 220 mL/minute blood flow, and, most of the time, an acetate buffer. Over the last few years we have progressively switched to bicarbonate.

The dose provided is large: the mean delivered Kt/V_{urea} calculated using the second generation Daugirdas method [21] is presently 2.0 per session. The delivered Kt/V has increased over the years as flat-plate Kiil dialyzers were replaced by larger area (1.5 – 2.1 m^2) cellulosic capillary dialyzers. The mean normalized protein catabolic rate is over 1.2. The mean protein and caloric intakes are 1.2 g/kg and 32 kcal/kg/day, respectively.

The patients are asked to maintain a low salt diet. No salt is added to the food, and processed food is avoided. Accordingly, the average sodium chloride intake is 5 g per day. As long as they stick to this low salt diet, patients are not requested to refrain from drinking. The low salt diet is initiated in the predialysis period whenever possible. The sodium restriction is strict during the first 2 months of dialysis and then progressively loosened as the patient loses his or her taste for salt. The mean interdialytic weight gain is 1.6 kg (i.e., 2.5% of mean dry weight).

No antihypertensive medication is used in over 95% of the patients after the second month of HD. It is crucial that during the initial few weeks of dialysis each patient undergo systematic antihypertensive treatment withdrawal in conjunction with the lowering of extracellular volume (ECV) to achieve "dry weight" and normotension.

The initial systematic step-by-step lowering of postdialysis weight (we call it the "probe") leads to intra- or postdialytic hypotension, the only feasible way to delineate the adequate postdialysis ECV. This must be clearly explained, so that the

patient understands and accepts this uncomfortable procedure. Antihypertensive medications are reintroduced only if needed, after a long, obstinate struggle for dry weight. Ambulatory blood pressure (BP) monitoring is of particular value at that stage to provide a true estimate of the full nyctohemeral BP value.

Later on, during maintenance treatment, the dry weight is systematically reevaluated after each dialysis session by the physician in charge, using a computerized, dialysis log chart featuring pre- and postdialysis weight, BP, and events occurring during the session. This mandatory continuous evaluation and adjustment of the dry weight is very important to achieving a normal ECV and normal BP.

While the method of treatment has remained unchanged over many years, the population has changed drastically. Splitting the population in five calendar cohorts from 1968 to 1997 permits survival analysis according to changing demographic and comorbid characteristics. Morbidity has been increasing over the years. From 1968 to 1989 changes were rather moderate (Table Ia). In contrast, in the last decade the patient case mix has worsened dramatically (Table Ib). The mean age at the start of dialysis increased from 36 years in 1968 to 64 years in 1997. During the same period, the prevalence of diabetes mellitus and nephrosclerosis in the incident population crept up from 5% to 53%, and the proportion of patients with cardiovascular comorbidity (myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, and peripheral vascular disease) increased from 6% to 61%.

Results

Mortality

Due to increasing risk factors, the crude mortality expressed as Kaplan-Meier survival curves has increased over time as shown for the five calendar cohorts (Fig. 1). But this compares patients who are almost free of comorbid conditions in the early cohorts with aged, sick patients with multiple comorbid conditions in the most recent cohorts. A fair and realistic view of mortality evolution must take into account the changing demographic and comorbid patterns of the population.

To achieve this, the patients' risk level must be stratified. The standardized mortality ratio (SMR) adjusts for age, race, sex, and cause of renal failure using the United States Renal Data System (USRDS) standard mortality table as the reference. For each calendar year the ratio of the observed to expected deaths is calculated. A value under 1.0 translates to a better-than-expected survival. The average observed mortality in Tassin is 45% of the expected value according to U.S. standards for similar patients. It has remained fairly stable over the calendar years (Table II) despite the worsening case mix.

Comparing Tassin mortality to the only available long-term French series of 4 – 5 hour HD [23] shows that mortality in the long-duration HD population is lower (52.4 vs 99 deaths per 1000 patient-years, $p < 0.001$). There is no difference in specific causes of mortality (infection, cancer, or others) between the two series, except for cardiovascular mortality, which is much lower on long-duration HD than on short-duration HD (19.8 vs 44.6 cardiovascular deaths per 1000 patient-years, $p < 0.001$).

TABLE IA Tassin prevalent population case mix evolution, 1968–97 (five cohorts)

Calendar year	*<1975*	*1976–79*	*1980–84*	*1985–89*	*1990–97*
Diabetes mellitus (%)	1	1	1	2	9
Nephrosclerosis (%)	4	8	8	7	12
Other/Unknown (%)	95	92	91	91	80
Age at start (years)	39.3	47.8	49.7	52.6	59.4
CV history (%)	10.2	22.6	26.4	39.5	59.5

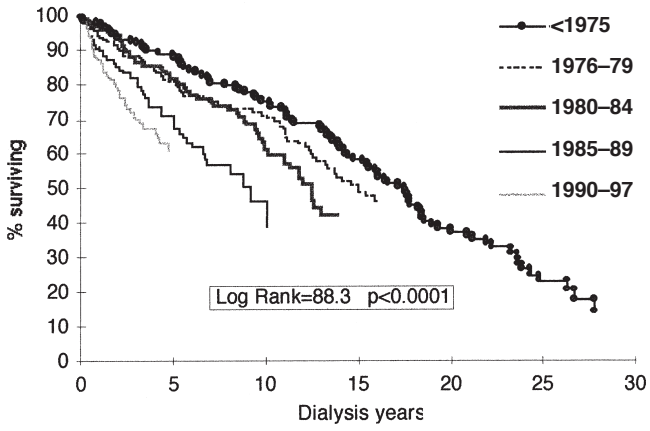

FIGURE 1 Kaplan-Meier survival curves of five calendar cohorts on long-duration (3 × 8 hours/week) dialysis in Tassin (1968 to 1997).

TABLE IB Tassin incident population case mix evolution, 1989–97

Calendar year	*1989*	*1990*	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*
Diabetes mellitus (%)	12.8	18.4	17.1	26.4	20.5	26.7	21.1	25.5	31.3
Nephrosclerosis (%)	25.6	21.1	24.4	22.6	25.6	20.0	28.1	26.0	21.9
Other/Unknown (%)	61.5	60.5	58.5	50.9	53.8	53.3	50.9	48.5	46.9
Age at start (years)	54.1	55.4	56	56.5	58.4	59	62	61.5	63.5
CV history (%)	41	46	47	50	54	57	55	58	61

CV history = cardiovascular history (myocardial infarction, angina, cerebrovascular accident, transient ischemic attach, peripheral ischemia).

TABLE II Tassin annual standardized mortality ratio, 1989–97

Calendar year	*O/E deaths*	*SMR*	*p Value*
1989	23/43.7	0.53	<0.005
1990	14/42.4	0.33	<0.001
1991	18/44.7	0.40	<0.001
1992	15/46.1	0.33	<0.001
1993	23/47.7	0.48	<0.001
1994	20/50.3	0.40	<0.001
1995	23/57	0.40	<0.001
1996	27/56.4	0.51	<0.001
1997	25/48.5	0.52	<0.001

O/E = observed/expected number; SMR = standardized mortality ratio.

If the Tassin long-duration dialysis population is split into two cohorts (equal in number) according to their median predialysis mean arterial pressure (MAP) (calculated over the entire time on HD therapy), and then the respective Kaplan-Meier survival is analyzed, the cohort of patients with the lowest MAP (mean = 89 mm Hg) has a significantly lower mortality ($p = 0.003$) than the cohort with a slightly higher MAP (mean = 107 mm Hg). The difference in survival is mainly explained by a lower cardiovascular mortality in the lower MAP cohort: 12.7 versus 28.1 cardiovascular deaths per 1000 patient-years ($p < 0.01$).

The Cox proportional hazard model was used to analyze the same patients' survival including demographic, comorbid, and treatment factors. Table III shows the influence of the following factors on mortality: age (range 12 – 91 years, mean 51.9 years), cause of renal failure, cardiovascular histories, middle molecule index (range 0.72 – 3.8, mean 1.57), Kt/V_{urea} (range 0.95 – 4.8, mean 1.79), MAP (range 50 – 155 mm Hg, mean 97 mm Hg), and serum albumin (range 20 – 55 g/L, mean 39 g/dL). Qualitative factors (cause of renal failure, cardiovascular histories), although not treatment related, are very powerful predictors of mortality (Table III). Diabetic patients have an 83.3% higher risk of death than nondiabetics; patients with a significant cardiovascular history when starting dialysis have an 87.9% higher mortality risk than patients free of cardiovascular disease. Some quantitative factors, either unrelated to treatment, such as age, or treatment related, such as middle molecule index, albumin concentration, and MAP, are also very powerful predictors of mortality. The relative risks based on the Cox model are most accurate closest to the mean values. For instance, for each year of age above 52 the mortality risk increases by 5% (relative risk = 1.050) or 50% for 10 years. Among treatment-related factors, Kt/V_{urea} per session is not a significant predictor of survival. In contrast, the more time-dependent middle molecule index is significantly related to mortality. For example, when the middle molecule index per session increases from 1.0 to 2.0, the risk of mortality decreases by 43.2% (relative risk of death 0.668). But the strongest predictors of mortality in our experience are serum albumin and predialysis MAP. For each g/dL increment of serum albumin above 39 g/L, the risk of mortality decreases by 2.9% (relative risk 0.971); for each mm Hg of predialysis MAP above 97 mm Hg, the risk of death increases by 3.4% (a 10 mm Hg higher predialysis MAP increases the risk of death by 34%).

Morbidity

An essential feature of long-duration HD is that it regularly achieves good BP control. The mean observed casual predialysis BP (128/79 mm Hg) is within the normal range advised by the 6th Joint National Committee on Blood Pressure [23]. Furthermore, ambulatory BP monitoring values [24] are also within normal range as defined by Staessen [25], at least for daytime (121/72 mm Hg) and circadian values (119/71 mm Hg). The nighttime values (118/67 mm Hg) are slightly higher than normal (106/64 mm Hg) due to the lack of a nocturnal dip in 50% of the patients.

On the other hand, intradialytic hypotensive episodes are less frequent on long- than on shorter-duration dialysis: 77 events per 1000 sessions on 8-hour dialysis versus 120 events per 1000 sessions on 5-hour dialyses ($p < 0.005$) in our own unit using a 5-hour dialysis [5] and 204 on 4-hour dialysis [25].

The relationship between ECV and BP is well illustrated by the first month of long-duration HD treatment (Fig. 2). Due to strong ultrafiltration and the strict low salt diet, the ECV expressed by postdialysis weight drops sharply during this period while predialysis MAP decreases more slowly over

TABLE III Tassin patient mortality using the Cox proportional hazard model

	Regression coefficient	*95% CI*	*RR*	*95% CI*	*p Value*
Age at start	0.049	(0.033, 0.067)	1.050	(1.033, 1.069)	<0.001
Diabetes	0.606	(0.131, 1.081)	1.833	(1.139, 2.947)	<0.01
CV history	0.631	(0.204, 1.057)	1.879	(1.226, 2.878)	<0.001
MM index	–0.404	(–0.681, –0.128)	0.668	(0.506, 0.880)	<0.01
Kt/V_{urea}	0.153	(–0.348, 0.675)	1.165	(0.706, 1.964)	NS
MAP	0.033	(0.011, 0.056)	1.034	(1.011, 1.057)	<0.005
Serum albumin	–0.029	(–0.064, 0.007)	0.971	(0.938, 0.993)	<0.001

CI = confidence interval; RR = relative risk; CV history = cardiovascular history (myocardial infarction, angina, cerebrovascular accident, transient ischemic attach, peripheral ischemia); MM = middle molecule; MAP = mean arterial pressure.

several months. The lag time between changes in ECV and BP [22] is a very important concept. The existence of this delay must be understood by the patient for him/her to accept the deliberate sustained decrease of his/her weight even though the BP does not "respond" immediately. Antihypertensive medications are stopped in over 95% patients within the first 2 months of long-duration HD. After 2 months of dialysis BP continues to decrease gradually, but weight typically increases (Fig. 2). This weight gain does not reflect an increase in ECV but a gain in fat and lean body mass due to the improved appetite and to anabolism following the start of maintenance dialysis.

The average predialysis hematocrit for the whole population (without blood transfusion or EPO) increased from an initial value of 23% at start to 28% at one year, 30% at 10 years, and 33% at 20 years. Presently, the hematocrit in the prevalent population is 33% with EPO used for 24% of the patients. The initial average serum albumin of 36.7 g/L (measured between two dialysis sessions) increased to 40.6 g/L at one year, 41.6 g/L at 2 years, and remained at this level after 20 years of dialysis.

Effects of switching the same group of patients from short- to long-duration HD and vice versa

One hundred and twenty-four transient HD patients were dialyzed in Tassin while awaiting a kidney transplant in Lyon. They were unselected. All had been treated for 6 months or more on a 5-hour or less HD schedule. Half of them received antihypertensive therapy.

Three months after changing to an 8-hour dialysis treatment, the postdialysis weight was reduced by a mean of 0.5 kg, predialysis MAP was almost back to normal (101 mm Hg), and antihypertensive medications were stopped in all but one patient. Thereafter predialysis MAP continued to decrease slowly but, due to anabolism, patients' weight increased progressively and plateaued after one year. Also in the first year, the mean predialysis hematocrit level increased from 24% to 29% without EPO or blood transfusions (27 patients required blood transfusions while on short-duration dialysis). Predialysis urea rose by 10% and creatinine by 25%.

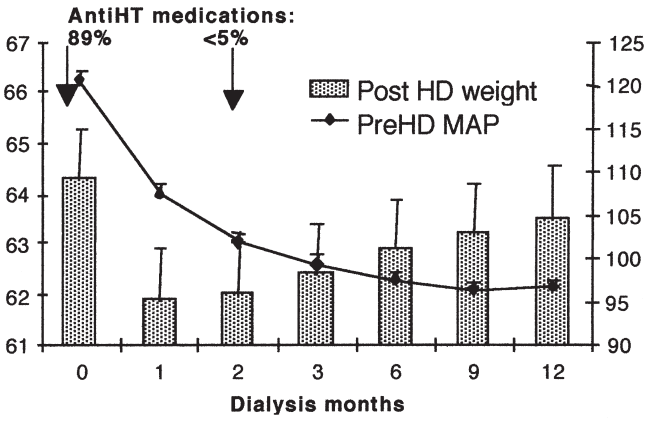

FIGURE 2 Evolution of postdialysis weight (kg) and predialysis arterial pressure (mm Hg) in 712 patients during the first 12 months of long-duration hemodialysis. AntiHT = antihypertension; HD = hemodialysis; MAP = mean arterial pressure.

Conversely, 49 Tassin 8-hour dialysis patients were switched to a 5-hour schedule. They were selected: all had been dialyzed 8 hours for at least 6 months. All were normotensive without antihypertensive medication. All had a blood access allowing for a dialysis blood flow of 300 mL/minute or more. Dialyzer area and blood flow were increased to maintain a similar Kt/V_{urea} when they were switched to the shorter schedule. After one year, the Kt/V delivered per session had changed only minimally (1.86 to 1.77). Predialysis MAP rose significantly by 10 mm Hg in spite of a mean 2.5 kg postdialysis weight reduction and the use of antihypertensive medications in 4 patients. On the other hand, predialysis urea and creatinine decreased by 8% and 19%, respectively. The mean hematocrit decreased from 31.5% to 27.5%, despite the fact that 3 patients were started on EPO.

Shortening the session time with only minimal change in the dialysis dose as judged by Kt/V_{urea} was, therefore, associated with impaired BP control and nutrition.

Discussion

The patient survival observed in Tassin using a long-duration dialysis schedule raises several questions: Is it due to favorable patient selection? Is it the result of a "center effect"? What is the impact of nutrition? What are the roles of ECV and BP control? What is the respective importance of HD dose and of session duration?

The Tassin patient case mix has progressively become comparable to what is described nowadays in the United States [11]. The change has been particularly obvious in the last 10 years. In 1997 the mean age at the start of dialysis was 63 years, the proportion of patients with diabetes or renal vascular disease was 55%, and a significant cardiovascular history was found in 60% of patients starting maintenance treatment. Even if a slightly favorable population selection bias remains in favor of Tassin, it cannot account for the large discrepancy in mortality (mortality is double in United States). In addition, despite the change in patient case mix, the SMR has remained stable over the last decade.

The results may be partly related to a "center effect," the combination of a low salt and high protein diet, close medical monitoring, and strict maintenance of dry body weight and BP. But all units where long-duration dialysis remains in use [27,28], as well as the centers that have started using it more recently [29], report the same excellent patient survival and low morbidity. The long, slow dialysis allows for excellent control of volume and BP, a satisfactory control of nutrition, correction of anemia with low doses of EPO, and good control of phosphatemia.

Why this difference in mortality between long-duration and the more conventional short-duration HD? Is survival better on long dialysis because the delivered Kt/V_{urea} is higher than in the usual short HD? Cross-sectional epidemiological data do suggest that the higher the Kt/V, the better. The longest survival rates have been reported in countries or registries using the highest doses (Japan); conversely, the shortest survival rates are in countries using the lowest doses (United States). Longitudinal data are even more convincing. In the United States the delivered Kt/V dose decrease from 1986 to 1989 was followed by a clear rise in mortality [10]. Conversely, the delivered Kt/V_{urea} increase since 1990 has been followed by a decrease in mortality [11]. Furthermore, when the delivered Kt/V_{urea} was deliberately increased in smaller but better controlled groups of patients, the mortality always decreased [13–16]. So, increasing the delivered Kt/V might be the best way of improving dialysis patient survival.

On the other hand, simple inspection of the Kt/V formula shows that for a given patient size (V), Kt/V depends on K and t. K depends on several factors, but blood flow, recirculation, and urea rebound in particular. If dialysis time is reduced, blood flow and dialysate flow must be increased and a high-efficiency dialyzer must be used to maintain the same Kt. High-efficiency dialysis tends to increase urea rebound, and high flow may increase recirculation. So, in operational conditions of dialysis it is very difficult to substantially increase the Kt/V_{urea} (over 1.8) without increasing the session time. Indeed, in the units previously mentioned where Kt/V was deliberately increased [13–16], in all cases this was achieved by increasing both K and t.

Time of dialysis affects much more than the Kt/V formula. It proportionally increases the larger solute clearances such as "middle molecules" [30] and the solutes with a low transcellular diffusibility such as phosphate more than the small solutes whose removal depends more on blood and dialysate flow.

A longer session time reduces HD "unphysiology" due to the acute fluctuations in the fluid compartment's volume and composition [31]. A longer dialysis session is slower and gentler, with less intradialytic morbidity as shown by our own and others' experience [29,32]. Fewer intradialytic symptoms provide a more comfortable dialysis thus providing one of the most efficient means of enhancing compliance [33]. From this point of view, increasing the session time appears to be the best way of increasing the dialysis prescription [34].

A longer dialysis session time also improves nutrition, which itself is strongly correlated with dialysis patient outcome [35]. Increasing the Kt/V_{urea} improves protein and calorie nutrition [36]. Appetite, on the other hand, seems to depend more on middle than on small molecular size solutes [37]. Other than sodium and to a minor degree potassium restrictions, the diet is liberal; the 8-hour dialysis patients are encouraged to eat a large amount of protein and calories, they do not need to use resins, and they do not receive vitamin supplementation. This liberal diet explains the important anabolic response after the onset of long dialysis [38].

The good ECV and BP control achieved are the most important features of long-duration HD. The development of shortened dialysis has led to an increased incidence of hypertension [39], cardiovascular morbidity, and mortality [17]. Shortened session times, with higher ultrafiltration rates and the large-scale use of antihypertensive medications, lead to a vicious circle [31,40,41] amplifying the BP variations and driving both intradialytic hypotension and interdialytic hypertension. Conversely, longer dialysis sessions allow better control of ECV expressed by achievement of dry weight and by normotension without antihypertensive medications. Our experience with modifying the dialysis schedule in the same group of patients confirms the key role of session time. Other groups using 8-hour dialysis in the past [42,43] and more recently [27,44] also achieved long-standing normotension.

In contrast to what has been reported for higher doses of dialysis which reduce all causes of mortality [45], longer dialysis sessions essentially decrease cardiovascular mortality. It is also noteworthy that cardiovascular mortality in Tassin has remained stable throughout the years while crude mortality has increased.

Arguments linking long survival to session time have been made by others. Two classic references [46,47] have been confirmed by a more recent one [48], showing that increasing the session time by a factor of 1.5 leads to a fourfold decrease in mortality. This study also found that the survival plateau was not reached at 5 hours of dialysis. So, dialysis time *per se* appears to be an important factor of survival.

The artificial kidney function cannot be reduced to Kt/V_{urea} any more than the native kidney function can be restricted to urea clearance rate. Optimal dialysis must fulfill several conditions, not just one. Increased dialysis time allows not only a good dose of dialysis, in terms of small and middle molecules, but also provides satisfactory nutrition, ECV, and BP control. This last point is essential: cardiovascular morbidity is by far the leading cause of death in dialysis patients. Only cardiovascular mortality is reduced by slow dialysis compared to shorter, now conventional dialysis. It is possible today to provide a satisfactory dose of dialysis within a few hours; it is much more difficult to achieve within the same time a satisfactory control of ECV and BP. This is especially true if the patient does not restrict salt, and if the sodium content of the dialysate is high [49,50]. For this reason, the dialysis session time should be essentially governed by the demand of BP control. In cases where normotension is easily achieved with long dialysis, it is often possible to reduce the session duration after some time; however, we do not decrease dialysis time to less than 5 hours.

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