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Clinical Study

Incremental Hemodialysis Schedule in Patients with Higher Residual Renal Function at the Start of Dialysis

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We present an observational study to evaluate a progressive schedule of dose of dialysis, starting with 2 HD/week, when the renal clearance of urea was equal to or greater than 2,5 mL/min/1,73 m^2 and the patient is in a stable clinical situation. From 2006 to 2011, 182 patients started hemodialysis in our center, of which 134 were included in the study. Residual renal function (RRF), Kt/V, eKru, nPCR, hemoglobin, weekly erythropoietin dose, and beta-2-microglobulin were determined at 6, 12, 18, 24, and 30 months after dialysis initiation. Seventy patients (52%) began with the progressive schedule of 2 HD/week and 64 (48%) patients began with the conventional thrice-weekly schedule (3 HD/week). The decline of RRF was lower in the group of 2 HD/week: 0,20 (0,02–0,53) versus 0,50 (0,14–1,08) mL/min/month (median and interquartile range, $P = 0,009$). No relationship was found between the decline rate and the basal RRF. Survival analysis did not show differences between both groups. Our experience demonstrates that patients with higher residual renal function may require less than conventional 3 HD sessions per week at the start of dialysis. Twice-weekly hemodialysis schedule is safe and cost-effective and may have additional benefit in maintaining the residual renal function.

1. Introduction

Dialysis dose in chronic patients treated with peritoneal dialysis is calculated using the sum of peritoneal clearance and residual renal function (RRF). Frequently, the peritoneal dialysis units start the treatment with a low peritoneal dose that is gradually increased afterwards to compensate the decline of RRF [1–4]. This incremental dialysis strategy is uncommon in hemodialysis units where it is habitual to start dialysis with the conventional thrice-weekly schedule (3 HD/week).

In 1985, Gotch and Keen [5] used the urea kinetic model to establish the fact that an adequate dialysis dose could be obtained using two sessions per week (2 HD/week) if renal clearance of urea was equal to or greater than 2,5 mL/min. However, although RRF is present in many patients starting hemodialysis, the 2 HD/week schedule has been scarcely considered.

In 2006, we established an incremental dialysis regimen at the start of renal replacement therapy, starting with 2 HD/week in such patients with higher residual renal function, considered a renal clearance urea equal to or greater than 2,5 mL/min. In a previous study we observed that the loss of glomerular filtration rate was lower in patients on the 2 HD/week regimen [6]. We present our 6 years of experience using this pattern with the aim of evaluating safety and clinical evolution of these patients.

2. Methods

We considered for the study all chronic renal patients who started dialysis in our unit from January 1, 2006, to December 31, 2011, and received dialysis for more than 3 months ($n = 182$). The patients transferred from peritoneal dialysis or other hemodialysis unit and the patients that were in anuria at the beginning of the dialysis therapy ($n = 48$) were excluded. So the number of patients finally included in the study was 134.

We routinely measure residual renal function, such as the arithmetic mean of the clearance of urea and creatinine

adjusted for body surface area. The clearance of urea and creatinine is estimated collecting urine 24 hours prior to the first dialysis session of the week and a sample of blood before dialysis [7, 8]. Basal urea and creatinine clearance are generally determined in the first week after starting dialysis. Subsequently, renal function is determined every 2 months until urine output is less than 100 mL/day.

All patients were treated with high-flux membranes and ultrapure dialysis fluid. The initial duration of dialysis was 3, 5, or 4 hours, according to whether the dry weight of the patient was lower or higher than 60 Kg.

The patients with a basal clearance of urea ≥2,5 mL min/1,73 m^2 and absence of clinical complications start the treatment with 2 HD/week. This pattern is maintained until the urea clearance falls below 2,5 mL/min/1,73 m^2 or clinical symptoms appear which advised increasing the frequency of dialysis. The patients with a basal clearance of urea <2,5 mL/min/1,73 m^2 or higher clearance but with symptomatic heart failure or sever hypertension start with three dialysis sessions a week. Patients treated with 2 HD/week receive 80 mg of furosemide daily.

The decline rates of the RRF and the daily urine volume for each patient were determined using a linear regression formula. In each patient it was calculated the differences between the basal values of RRF and the daily urinary volume obtained immediately before the loss of RRF (when the urinary output was lower of 100 mL/day), or the last values obtained before the end of the hemodialysis therapy by kidney transplant, death, recovery of the renal function, transfer to peritoneal dialysis, or reach the date of the end of the study. In the group of 2 HD/week also was considered as the last determination of RRF just before changing to 3 HD/week. The difference between the basal and the last values of each patient was divided by the time (in months) from the basal to the last determination. As a result, we obtained a RRF decline rate (in mL/min/month) and a daily urinary volume decline rate (in mL/month).

The dose of dialysis was calculated with the single-pool Kt/V of urea using the second generation Daugirdas formula (Kt/V dialysis). The Kt/V total was calculated by adding the renal urea clearance to the Kt/V of dialysis, as described by Gotch [9]. The equivalent renal urea clearance (eKru) is defined as the ratio between the urea generation rate and the time-average urea concentration [10]. The urea generation rate was determined according to the method of Depner et al. [11] and the time-average urea concentration using the formula of Lowrie and Teehan [12]. The normalized protein catabolic rate (nPCR) was calculated with the formula of Borah modified by Sargent [13]. Residual renal function, Kt/V, eKru, nPCR, serum hemoglobin concentration (g/dL), weekly erythropoietin dose (IU/week/kg), and predialysis beta-2-microglobulin (B2M) concentration were determined at 6, 12, 18, 24, and 30 months after dialysis initiation. The RRF was considered zero in patients with a urinary output <100 mL/day. Comorbidity at dialysis initiation was measured by the Charlson comorbidity index [14].

The follow-up period includes the period from the onset of dialysis to the end of hemodialysis treatment for any reason (transplant, recovery renal function, transfer to peritoneal dialysis, or death), or until the date of finalization of the study on June 30, 2012. The rate of hospitalization was analyzed from October 1, 2010, to June 30, 2012.

The study was approved by the local medical ethic committee and patients signed informed consent before beginning treatment with dialysis.

2.1. Statistical Analysis. The Kolmogorov-Smirnov test was used to test the normality of the data. Results are presented as mean ± standard deviation for normally distributed data. The decline of residual renal function and the volume of urine output and the total days of hospitalization did not follow a normal distribution so the results were expressed as the median and the interquartile range (IQR). Comparison of continuous variables was carried out using Student's t-test for independent samples with normal distribution or the Mann-Whitney U-test in samples that do not follow a normal distribution. The chi-square and the Fisher tests were used to compare noncontinuous variables. The relationship between different clinical parameters and the decline of residual renal function and urine output was assessed using the Spearman correlation test. We also calculated the probability of survival of the patients using the Kaplan-Meier curves. The patients who started with 2 HD/week were not censored when they began three sessions per week in order to observe the complete evolution of this population. The patients were censored at the time of the transplant, the recovery of renal function, the transfer to dialysis peritoneal, or the date of end of study.

3. Results

Seventy patients (52%) began dialysis with 2 HD/week for maintaining a clearance of urea ≥2,5 mL/min/1,73 m^2 and absence of clinical complications and 64 (48%) patients began dialysis with the usual pattern of three sessions a week. Of the 64 patients who started with 3 HD/week, 31 had a clearance of urea ≥2,5 mL min/1,73 m^2, but their doctor decided to start with 3 HD/week due to clinical complications such as heart failure, hypertension, or overhydration. Demographic and clinical characteristics of the patients at the start of hemodialysis are summarized in Table 1. We observed that daily urinary volume and GFR (glomerular filtration rate) are higher in the group of 2 HD/week. The range of GFR was 2–12,6 mL/min and 0,2–13,6 mL/min in patients who started 2- and 3 HD/week, respectively.

Other parameters do not show differences statistically significant between both groups of patients.

The daily urinary volume decline and the RRF decline rates are shown in Table 2.

The decline in RRF was lower in the group of 2 HD/week. The RRF decline rate was not related to basal RRF ($P = 0,253$), age, body mass index, or the Charlson comorbidity index.

Figure 1 shows the glomerular filtration rate (GFR) (mL/min/1,73 m^2), expressed as median and interquartile. The GFR of patients who began with 2 HD/week was higher during the first two years of treatment with hemodialysis (Figure 1).

Table 1: Baseline data of the patients.

	Group 2 HD/week	Group 3 HD/week	
N	70 (52%)	64 (48%)	
Age (years)	62,2 ± 15,1	62,6 ± 11,9	$P = 0{,}847$
Male gender	49 (70%)	50 (78%)	$P = 0{,}382$
Primary renal diagnosis:			
Glomerulonephritis	12 (17,1%)	8 (12,5%)	
Renal vascular disease	8 (11,4%)	10 (15,6%)	
Interstitial nephropathy	14 (20%)	10 (15,6%)	
Diabetic nephropathy	14 (20%)	13 (20,3%)	$P = 0{,}296$
Polycystic kidney disease	7 (10%)	6 (9,4%)	
Other	10 (14,3%)	10 (15,6%)	
Unknown	5 (7,1%)	7 (10,9%)	
Kidney transplant failure	11 (16%)	15 (23%)	$P = 0{,}362$
Body mass index (kg/m^2)	25,9 ± 5,1	25 ± 4,8	$P = 0{,}294$
Charlson index	6,2 ± 2,7	6,6 ± 2,5	$P = 0{,}362$
Arteriovenous fistula as initial vascular access	41 (59%)	33 (51%)	$P = 0{,}461$
Daily urinary volume (mL)	1618 ± 832	1153 ± 676	$P < 0{,}001$
GFR (mL/min/1,73 m^2)	6,35 ± 2,35	5,22 ± 2,74	$P = 0{,}010$

Table 2: Daily urinary volume decline and RRF decline rate.

	Group 2 HD/week	Group 3 HD/week	
Daily urine volume decline rate (mL/month)	61 (0–171)	98 (44–228)	$P = 0{,}016$
RRF decline rate (mL/min/month)	0,20 (0,02–0,53)	0,50 (0,14–1,08)	$P = 0{,}009$

Values are expressed as median and IQR.

Of the 70 patients who began 2 HD/week, 16 were transplanted, 3 were transferred to peritoneal dialysis, 4 died, 31 went to 3 HD/week, and 10 remained in 2 HD/week till the end of the track. Six patients were able to discontinue the treatment with hemodialysis by improving the RRF, but all of them have advanced chronic renal failure and returned to hemodialysis few months later. Of the 31 patients who went to three sessions per week, 7 were transplanted, 8 died, and 16 continued on hemodialysis till the end of the study.

Of the 64 patients who began 3 HD/week, 15 were transplanted, 8 were transferred to peritoneal dialysis, 2 moved to another dialysis unit, 16 died, 16 remained in 3 dialysis sessions a week, and 7 were transferred to two dialysis sessions per week by maintaining a clearance of urea ≥2,5 mL/min/1,73 m^2 and the symptoms of heart failure or overload had disappeared that made it advisable to begin treatment

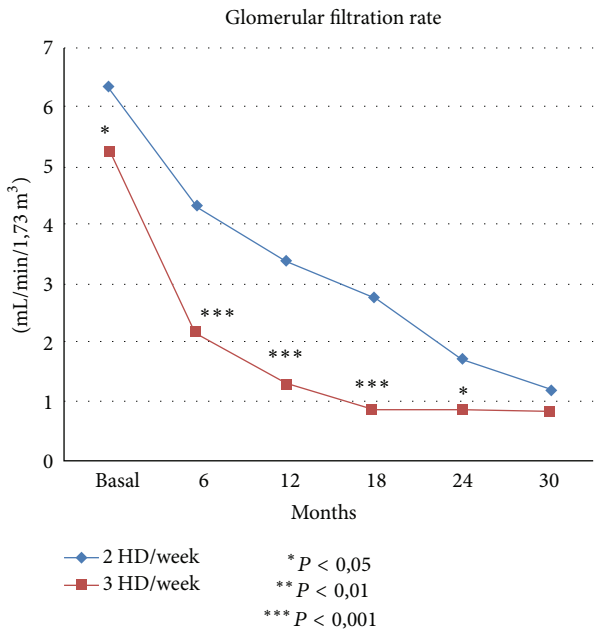

Figure 1: Glomerular filtration rate (mL/min/1,73 m^2), expressed as median and interquartile.

with 3 sessions of dialysis. Of the 7 patients transferred to 2 HD/week, 3 discontinued temporally hemodialysis by a transient recovery of renal function, 2 were transplanted, and 2 continue on dialysis with the same scheme of treatment.

The number of patients with the twice-weekly hemodialysis schedule, the prevalence of patients in anuria, the dose of dialysis, the hemoglobin concentration, the weekly doses of erythropoietin, and the beta-2-microglobulin concentration over evolution are shown in Table 3.

The 35% of the patients who started 2 HD/week continued with this schedule 24 months after starting dialysis. The number of patients in anuria was significantly higher in the group with 3 HD/week, while the RRF and the Kt/V total were significantly higher in the group of 2 HD/week. There were no significant differences in the Kt/V dialysis, eKru, and nPCR between the two groups. Hemoglobin concentration was similar in both groups, but the weekly dose of erythropoietin was significantly lower in patients that began with 2 HD/week. Similarly, B2-microglobulin concentration was also significantly lower in this group.

The total follow-up on hemodialysis of patients who started with 2 HD/week was $18,3 \pm 12,8$ months (1283 patients-month) and $23,3 \pm 19,8$ (1490 patients-month) in patients who started with 3 HD/week. Patients that began with 2 HD/week spent 734 patients-month in this pattern (57% of their total time on hemodialysis). The number of dialysis sessions performed in the 2 HD/week group was 13498. If these patients had been treated with 3 sessions per week since the beginning, they would have received 16679 dialysis sessions, which represents a saving of 3181 sessions (19%).

Survival analysis did not show significant differences between both groups (log-rank, chi-square: 0,587, $P = 0,444$), and the causes of death were also similar. Four patients

Table 3: Clinical and analytical data in twice-weekly and three-weekly hemodialysis schedule along the follow-up period.

		Basal	6 months	12 months	18 months	24 months	30 months
Group 2 HD/week	On hemodialysis	70	61	41	32	20	14
	On 2 HD/week	70	49 (80%)	23 (56%)	12 (38%)	7 (35%)	2 (14%)
	Anuric patients	0	5 (8%)	11 (27%)	12 (38%)	13 (65%)	11 (79%)
	RRF (mL/min/1,73 m^2)	6,35 ± 2,35	4,31 ± 2,95	3,39 ± 2,98	2,75 ± 1,96	1,71 ± 1,57	1,18 ± 2,56
	Kt/V dialysis	—	1,42 ± 0,28	1,48 ± 0,27	1,45 ± 0,27	1,50 ± 0,34	1,58 ± 0,27
	Kt/V total	—	2,13 ± 0,54	1,96 ± 0,44	1,88 ± 0,49	1,81 ± 0,39	1,75 ± 0,36
	nPCR (g/kg/day)	—	1,02 ± 0,18	0,97 ± 0,24	1,01 ± 0,27	1,08 ± 0,23	1,07 ± 0,24
	eKru (mL/min)	—	6,39 ± 1,30	6,12 ± 1,88	6,45 ± 1,76	6,65 ± 1,33	6,67 ± 1,20
	Hemoglobin level (g/dL)	10,6 ± 1,3	11,5 ± 1,3	11,4 ± 1	11,5 ± 1,3	11,4 ± 1,1	11,5 ± 0,9
	Erythropoietin dose (IU/week/kg)	124 ± 76	119 ± 102	99 ± 74	113 ± 99	109 ± 116	116 ± 114
	B2M level (mg/L)	19,3 ± 7,4	23,7 ± 9,8	26,2 ± 11,1	29,7 ± 14,7	32,9 ± 15,1	33,9 ± 8,7
Group 3 HD/week	On hemodialysis	64	51	42	33	23	18
	Anuric patients	0	16 (31%)**	25 (60%)**	23 (70%)*	18 (78%)	14 (78%)
	RRF (mL/min/1,73 m^2)	5,22 ± 2,74*	2,13 ± 1,66***	1,29 ± 1,28***	0,85 ± 0,76***	0,84 ± 1,20*	0,82 ± 1,89
	Kt/V dialysis	—	1,44 ± 0,32	1,50 ± 0,21	1,53 ± 0,24	1,44 ± 0,21	1,53 ± 0,16
	Kt/V total	—	1,57 ± 0,34***	1,58 ± 0,23***	1,59 ± 0,25**	1,51 ± 0,23**	1,61 ± 0,23
	nPCR (g/kg/day)	—	1,06 ± 0,26	1,03 ± 0,23	0,96 ± 0,15	1,07 ± 0,23	0,92 ± 0,15
	eKru (mL/min)	—	6,54 ± 1,24	6,42 ± 1,65	6,80 ± 1,45	6,65 ± 0,93	6,62 ± 1,60
	Hemoglobin level (g/dL)	9,9 ± 1,4**	11,3 ± 1,3	11,4 ± 1,4	11,1 ± 1,4	11,3 ± 1,5	11,5 ± 1,3
	Erythropoietin dose (IU/week/kg)	143 ± 76	163 ± 100*	158 ± 111**	178 ± 107*	151 ± 105	145 ± 83
	B2M level (mg/L)	26,2 ± 9,2***	32,2 ± 11***	35 ± 9,9***	37,7 ± 14,1*	39,7 ± 15,2	38,8 ± 13,2

*$P < 0{,}05$; **$P < 0{,}01$; ***$P < 0{,}001$ (between 2 HD/week and 3 HD/week groups).

died during the treatment with two hemodialysis sessions per week but the cause of the death was not related to the hemodialysis schedule (multiple myeloma, vascular dementia, pneumonia associated with chronic obstructive pulmonary disease, and abdominal sepsis secondary to diverticulitis).

The rate of hospitalization was analyzed from October 1, 2010, to June 30, 2012. During this period of time 41 patients of the group of 2 HD/week and 26 patients of the group of 3 HD/week were treated. The rate of all-cause hospital admissions was 61% (25/41) and 88% (23/26), respectively ($P = 0,011$). Hospitalization time was 4 (0–15) and 11 (2–14) days/patient-years in the 2- and 3 HD/week groups, respectively (median and IQR, $P = 0,068$). Vascular access dysfunction was the cause of hospitalization in 6 patients of the group of 2 HD/week (15%) and in 8 patients of the group of 3 HD/week (31%) ($P = 0,071$).

4. Discussion

The treatment with three hemodialysis sessions per week is the usual pattern that clinical guidelines recommended for treating patients with chronic renal failure [15, 16], and most patients start dialysis with this schedule without taking into account its residual renal function. In 2006 we introduced an incremental dose of hemodialysis, similar to the practice carried out by some units of peritoneal dialysis. According to our protocol, patients with a clearance of urea ≥2,5 mL/min/1,73 m^2 and stable clinical situation began treatment with 2 HD/week. In the present study we report the experience of 6 years to implement this protocol.

Of 134 patients included in the study, 70 (52%) started dialysis with a twice-weekly hemodialysis schedule and 65 patients (48%) started dialysis with the conventional thrice-weekly hemodialysis schedule. There were no differences in age, gender, primary kidney disease, prior transplantation, body mass index, type of vascular access, or comorbidity index between both groups.

The eKru is a parameter commonly used to compare the dose of dialysis between different schedules of hemodialysis [10]. According to this parameter, patients of both groups received similar dose of dialysis along the follow-up period. The Kt/V per dialysis session was also similar in both groups; however the Kt/V total was higher in the group of 2 HD/week as a result of a greater residual renal function. The nPCR did not show significant differences between both groups at any point in the evolution.

According to our selection criteria, baseline renal function was greater in the 2 HD/week group. The two groups are not homogeneous and the difference in the basal RRF could justify the higher residual renal function observed in the group 2 HD/week during the first two years of evolution.

However, we have also analyzed the decline of RRF expressed in mL/month, and we found that the decline of RRF was lower in the 2 HD/week and it does not depend on basal value. This data supports our hypothesis that the pattern of 2 HD/week contributes to better preserving RRF.

The importance of maintaining RRF in hemodialysis patients is very important since different studies have shown that preserving residual kidney function is associated with improved survival, and it is considered as an index of adequacy [17–20].

Other relevant clinical findings were that patients starting dialysis with two sessions per week had a better control of anemia. Although serum hemoglobin level was similar in both group of patients, weekly erythropoietin dose was significantly lower in patients with 2 HD/week, even at 18 months of having started dialysis. This fact could be explained due to the beneficial effect on anemia attributed to the preservation of the RRF [21–23].

The increase in the B2M is associated with worse prognosis in the HEMO study [24]. Although levels of B2M were lower in the 2 HD/week patients, probably due to higher RRF [25–27], the mortality and causes of death were similar in both groups. Only 4 patients died when they received two hemodialysis sessions per week and the cause of the death could not be attributed to the hemodialysis schedule.

The twice-weekly hemodialysis regimen is scarcely used, but Lin et al. reported the outcome of 23 prevalent dialysis patients dialyzed two times per week that showed similar results. The twice-weekly group had a slower decline of RRF, had lower serum B2M, and required fewer admissions [27].

In conclusion, our experience demonstrates that patients with higher residual renal function may require less than conventional 3 HD sessions per week at the start of dialysis. Twice-weekly hemodialysis schedule is safe and cost-effective and may have additional benefit in maintaining the residual renal function.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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