

The Clinical Impact of Increasing the Hemodialysis Dose

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Good evidence suggests that improvements in dialysis efficiency reduce morbidity and mortality of hemodialysis (HD) patients. Dialysis efficiency has also been related to better control of arterial blood pressure (BP), anemia, and serum phosphorus levels, and to improvement in patients' nutritional status.

Over a 2-year period, the present self-controlled study of 34 HD patients (23 men, 11 women; age, 52.6 ± 14.5 years; HD duration, 55.9 ± 61.2 months) looked at the effect on clinical and laboratory parameters of increasing the delivered dialysis dose under a strict dry-weight policy. Dialysis dose was increased without increasing dialysis time and frequency.

A statistically significant increase was seen in delivered HD dose: the urea reduction ratio (URR) increased to $60\% \pm 10\%$ from $52\% \pm 8\%$, and then to $71\% \pm 7\%$ ($p < 0.001$); Kt/V_{urea} increased to 1.22 ± 0.28 from 0.93 ± 0.19 , and then to 1.55 ± 0.29 ($p < 0.001$). A statistically significant increase in hemoglobin concentration also occurred—to 10.8 ± 1.9 g/dL from 10.4 ± 1.7 g/dL, and then to 11.0 ± 1.3 g/dL ($p < 0.05$ as compared to baseline)—with no significant difference in weekly erythropoietin dose.

Statistically significant decreases occurred in the systolic and diastolic blood pressures during the first year; they then remained unchanged. Systolic blood pressure decreased to 131 ± 23 mmHg from 147 ± 24 mmHg ($p < 0.001$); diastolic blood pressure decreased to 65 ± 11 mmHg from 73 ± 12 mmHg ($p < 0.001$). Serum albumin increased insignificantly to 4.4 ± 0.4 g/dL from 4.3 ± 0.4 g/dL, and then significantly to 4.6 ± 0.3 g/dL ($p = 0.002$ as compared to both previous values). Normalized protein catabolic rate increased significantly to 1.16 ± 0.15 g/kg/day from 0.93 ± 0.16 g/kg/day ($p < 0.001$), and then to 1.20 ± 0.17 g/kg/day ($p < 0.001$ as compared to baseline).

We conclude that the increases achieved in average Kt/V_{urea} per hemodialysis session by increasing dialyzer membrane area, and blood and dialysate flows, without increasing dialysis time above 4 hours, in patients hemodialyzed thrice weekly, coupled with strict dry-weight policy, resulted in improvements in hypertension, nutritional status, and anemia.

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Introduction

Until the early 1980s, adequacy of dialysis had been mostly an empirical assessment based on the clinical status and blood chemistries of patients with end-stage renal disease (ESRD). The National Cooperative Dialysis Study (NCDS), the first study correlating the dose of dialysis with the clinical outcome of patients, triggered the quest for an objective assessment of dialysis adequacy [1]. Gotch and Sargent suggested Kt/V_{urea} as a reliable index of the delivered dialysis dose that could be used to estimate dialysis adequacy [2].

The therapeutic Kt/V_{urea} target of 0.9–1.0, posed by Gotch and Sargent, has not provided the expected results regarding the survival of dialyzed patients. Studies published in the 1990s established a strong negative correlation between dialysis dose and the morbidity and mortality of patients; higher therapeutic targets for delivered dialysis dose were suggested thereafter [3–8]. Many of these studies reported how increasing the dialysis dose affected clinical parameters such as anemia [9], hypertension [10,11], nutritional status [12,13], and serum phosphorus control [11].

In the present study, we investigated the impact of an increase in delivered dialysis dose on the clinical status of hemodialyzed patients.

Material and methods

The present study began in 1998 when the assessment of delivered dialysis dose was established as a routine practice in our dialysis unit. Until then, a roughly uniform treatment was administered to the patients instead: 4-hour dialysis sessions three times weekly, using moderate blood flow rates and hollow-fiber, synthetically modified cellulose membrane dialyzers of moderate efficiency (as practiced in the acetate era), although bicarbonate dialysis and ultrafiltration controllers were uniformly used. The iron supplementation strategy remained unchanged throughout the study.

From the beginning of the study, the dialysis dose delivered to every patient was measured regularly. Subsequently, the dialysis prescription was changed with a view to increasing the delivered dose. The changes (presented in Table I) included incremental increases in blood flow rate, dialyzer surface area, and, finally, dialysate flow rate (in the machines providing this possibility). Dialysis time was left unchanged

TABLE I Dialysis prescription.

Parameters	Baseline	12 months	24 months
Dialyzer surface area (m ²)	1.15±0.1	1.57±0.3 ^a	1.70±0.2 ^a
Blood flow rate (mL/min)	240±35	330±40 ^a	410±70 ^a
Dialysate flow rate (mL/min)	500	500	560±110
Dialysis time (h)	4	4	4

^a $p < 0.05$ vs baseline.

from the previous standard of 4 hours. We used dialyzer models BLF 12GW and BLF 16GW in the first phase of the study, and BLF 18GW almost exclusively in the second phase (NIKKISO Ltd., Tokyo, Japan). The type of membrane did not change from synthetically modified cellulose.

The observations were conducted in two time periods. During the first period (0 – 12 months), the dialysis dose was increased to achieve the therapeutic Kt/V_{urea} target of 1.2, while a strict dry-weight policy was followed. During the second period (12 – 24 months), an effort was made to deliver the highest possible dialysis dose for each patient.

When the study began, 44 chronic HD patients were being treated in our unit. During the following 2 years, 10 patients dropped out [4 died, 4 underwent transplantation, 1 was transferred to continuous ambulatory peritoneal dialysis (CAPD), and 1 moved to another unit] and 21 new ESRD patients started in our hemodialysis program. Two patients died during the first phase of the study, and two during the second phase. Only those patients dialyzed throughout the full 2-year study period are presented—that is, 34 patients: 23 men and 11 women, aged 52.6 ± 14.5 years (median: 56 years) on maintenance dialysis for 55.9 ± 61.2 months (median: 32 months). Parameters assessed included dialysis efficiency, hemoglobin (Hb), weekly dose of erythropoietin (EPO), body weight, blood pressure, antihypertensive medications, normalized protein catabolic rate (nPCR), serum albumin (measured using the bromocresol green method), phosphorus levels, and the consumed quantity of phosphate binders (as tablets per day).

Measurements were performed monthly at midweek sessions. The efficiency assessment included the urea reduction ratio (URR) and Kt/V_{urea} calculated by the Daugirdas logarithmic formula [14]. Post-dialysis urea was measured at the completion of the programmed dialysis time in a blood sample drawn from the arterial needle after slow flow for at least 2 minutes (blood pump set at 50 mL/min). The nPCR assessment was based on nomograms [15].

In tables, variables are presented as mean \pm standard deviation. Comparisons were performed using the Student paired t -test and the chi-square test; p values less than 0.05 were considered significant.

Results

The increase in delivered dialysis dose was statistically significant for both periods (Table II). The URR, $52\% \pm 8\%$ at the beginning, increased to $60\% \pm 10\%$ at the end of first

period ($p < 0.001$), and even further to $71\% \pm 7\%$ at the end of second period ($p < 0.001$ as compared to both previous values). The Kt/V_{urea} increased to 1.22 ± 0.28 at 12 months from 0.93 ± 0.19 at baseline ($p < 0.001$) and to 1.55 ± 0.29 at 24 months ($p < 0.001$ as compared to both previous values).

A statistically significant increase in hemoglobin to 11.0 ± 1.3 g/dL at the end of the study from 10.4 ± 1.7 g/dL at the beginning ($p < 0.05$) was seen. Meanwhile, the slight decrease in weekly EPO dose from the beginning of the study to the end was not statistically significant (to 4300 ± 4000 U/week from 4700 ± 3800 U/week, $p = 0.294$).

Body weight decreased statistically significantly during the first period (to 65.1 ± 11.1 kg from 67.8 ± 11.9 kg, $p < 0.001$); the small increase during the second period (to 65.6 ± 10.9 kg) was not significant. Systolic blood pressure (SBP) decreased significantly during the first period (to 131 ± 23 mmHg from 147 ± 24 mmHg, $p < 0.001$). No significant change was recorded thereafter (133 ± 25 mmHg). Comparable changes were noted in diastolic blood pressure (DBP), which dropped from 73 ± 12 mmHg at baseline to 65 ± 11 mmHg at the end of first period ($p < 0.001$), and then increased insignificantly to 66 ± 13 mmHg at the end of study. Antihypertensive medication was being given to 17 patients (50%) at the start of study, to 14 patients (41%) at the end of the first period, and to 7 patients (21%) at the end of the study. The final percentage was statistically significantly lower as compared with the initial one ($p = 0.022$).

Serum albumin did not change significantly during the first period (to 4.4 ± 0.4 g/dL from 4.3 ± 0.4 g/dL, $p = 0.636$), but it increased statistically significantly during the second period (to 4.6 ± 0.3 g/dL, $p = 0.002$ as compared to both previous values). A statistically significant increase in nPCR was seen during the first period (to 1.16 ± 0.15 g/kg/day from 0.93 ± 0.16 g/kg/day, $p < 0.001$); a further increase during the second period to 1.2 ± 0.17 g/kg/day was nonsignificant.

Serum phosphorus levels underwent a statistically significant decrease during the first period (to 5.1 ± 1.7 mg/dL from

TABLE II Results.

Parameter	Baseline	12 Months	24 Months
Kt/V_{urea}	0.93±0.19	1.22±0.28 ^a	1.55±0.29 ^{a,b}
Urea reduction ratio (%)	52±8	60±10 ^a	71±7 ^{a,b}
Hemoglobin (g/dL)	10.4±1.7	10.8±1.9	11.0±1.3 ^a
Erythropoietin dose (U/week)	4700±3800	5300±4300	4300±4000
Body weight (kg)	67.8±11.9	65.1±11.1 ^a	65.6±10.9
Systolic blood pressure (mmHg)	147±24	131±23 ^a	133±25 ^a
Diastolic blood pressure (mmHg)	73±12	65±11 ^a	66±13 ^a
Antihypertensive treatment (n)	17/34 (50%)	14/34 (41%)	7/34 (21%) ^a
nPCR (g/kg/day)	0.93±0.16	1.16±0.15 ^a	1.20±0.17 ^a
Serum albumin (g/dL)	4.3±0.4	4.4±0.4	4.6±0.3 ^{a,b}
Serum phosphorus (mg/dL)	5.9±1.5	5.1±1.7 ^a	5.3±1.7 ^a
Phosphate binders (tablets/day)	7.0±3.4	5.4±3 ^a	4.1±2.7 ^a

^a $p < 0.05$ vs baseline.

^b $p < 0.05$ vs 12 months.

nPCR = normalized protein catabolic rate.

5.9 ± 1.5 mg/dL, $p = 0.003$); the change during the second period (to 5.3 ± 1.7 g/dL, $p = 0.664$) was not significant. A statistically significant decrease in the consumption of phosphate binders, dictated by serum phosphorus levels, occurred during the first period (to 5.4 ± 3.0 tablets per patient per day from 7.0 ± 3.4 tablets per patient per day, $p = 0.002$). A further decrease (to 4.1 ± 2.7 tablets per patient per day) during the second period was not significant ($p = 0.053$).

Discussion

Dialysis dose measured by removal of urea and expressed as its clearance (K) multiplied by dialysis time (t) and divided by urea distribution volume (V)—that is, the Kt/V_{urea} —has been of increasing interest since the early 1980s, when the results of NCDS were published [2]. The ideal delivered dose of dialysis, which provides the longest possible survival of patients, is still a matter of controversy. Hakim *et al.* [4] suggested a target delivered $Kt/V_{\text{urea}} \geq 1.4$. Collins *et al.* [7] proposed a $Kt/V_{\text{urea}} \geq 1.4$ for patients with diabetes and between 1.2 and 1.4 for non diabetic patients. Others have suggested even higher targets [5,11].

In the present study, the increase in delivered dialysis dose during the first period attained the goal of a Kt/V approximately equal to 1.2—that is, the National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF–DOQI) recommendation [14]. During the second period, the objective was to deliver the greatest possible dialysis dose to each patient without increasing dialysis time and frequency. The impact of this two-stage increase in dialysis dose on clinical and laboratory parameters of patients was separately evaluated.

The increase in dialysis dose resulted in an improvement in anemia without an incremental increase in EPO dose and without a change in iron supplementation. This finding echoes the observations of other authors [9], supporting the view that substances in the uremic environment either inhibit erythropoiesis [16] or induce hemolysis [17], and that intensive dialysis eliminates those substances effectively.

The statistically significant decrease in blood pressure noticed during the first period of the study should not be attributed to the increased dialysis; rather, we think it is the effect of the strict dry-weight policy adopted during this period. This hypothesis is supported by the statistically significant decrease in the body weight of patients during this period. However, the maintenance of normal blood pressure thereafter without further decrease of body weight and with a statistically significant decrease in antihypertensive medications may suggest an important role for increased dialysis in effective blood pressure control. Others have reported similar findings with increased dialysis doses associated with increases in dialysis time, and increases in both frequency and time [11,18]. Substances eliminated by dialysis are also speculated to accumulate in the interdialytic interval and to induce a volume-independent increase in blood pressure [10,19]. This view is consistent with the fact that intensive dialysis results in better control of blood pressure. Some authors, however,

found no correlation between Kt/V_{urea} and blood pressure [20,21], but found a strong correlation between blood pressure and interdialytic weight gain [22].

The increase in delivered dialysis dose was also coupled with an increase in nPCR and serum albumin levels. Positive correlation has already been described between nPCR and Kt/V_{urea} [12,23] and between serum albumin and Kt/V_{urea} [6,13]. Some studies, however, conclude that no correlation exists between serum albumin levels and dialysis adequacy indexes, and argue that the relationship between Kt/V and nPCR is fictitious, a consequence of shared mathematical formulas used in the calculation of both parameters [8]. Authors refuting the mathematical coupling between these indexes insist that the increase in dialysis dose results in better appetite in dialysis patients and a subsequent improvement in nutrition [6,24,25].

According to the literature, increasing the dialysis dose per session without increasing the frequency of sessions does not result in better serum phosphorus control [11,26]. Patients in our study had a statistically significant decrease in serum phosphorus level and phosphate binders only during the first period of the study. The further increase in dialysis dose achieved during the second period had no significant effect on hyperphosphatemia in our patients. Thus, we presume a limited effect of dialysis dose (as measured by Kt/V_{urea}) on serum phosphorus control.

Conclusion

We conclude that increasing the average Kt/V_{urea} to 1.22 from 0.93 per hemodialysis session in patients hemodialyzed thrice weekly (by increasing the dialyzer membrane area and the blood and dialysate flows, without increasing dialysis time above 4 hours), coupled with a strict dry-weight policy, results in improvement of hypertension and nutritional status. Further increasing Kt/V_{urea} to 1.55 from 1.22 under the same conditions improves anemia and results in an increase in serum albumin concentration.

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