ORIGINAL ARTICLES

Phosphorus Clearance Using Two Hemodialyzers Placed in Parallel

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Control of hyperphosphatemia is a major goal in patients with end-stage renal disease. However, removal of retained inorganic phosphorus during hemodialysis remains a major problem. We compared clearances and total phosphate removal in large patients treated with two F-80 dialyzers (Fresenius Medical Care of North America, Lexington, MA, U.S.A.) placed in parallel, and small patients dialyzed with a single F-80 dialyzer (SD). Clearances were obtained using total dialysate collections. Eight dialysate collections (5 patients) using double parallel dialyzers (DD group) were compared with 5 dialysate collections (4 patients) using single dialyzers (SD group). Blood and dialysate flow rates and time of dialysis treatment were identical between the groups.

*The DD group's Kt/V_{urea} was 1.46 ± 0.13; SD group's Kt/V_{urea} was 1.35 ± 0.09 (*p *= 0.2). Absolute phosphorus removal was 1594 ± 300 mg for the DD group, compared to 1108 ± 285 mg in the SD group (*p *= 0.03). Urea clearance in the DD group was 285 ± 25 mL/minute and 251 ± 27 mL/min in the SD group (*p *= 0.082). Phosphorus clearance was 178 ± 32 mL/min in the DD group and 149 ± 38 mL/min in the SD group (*p *= 0.039). There was no correlation between phosphorus clearance and dialyzer reuse. The bulk of phosphorus removal was achieved during the first 2 hours of hemodialysis. This finding is consistent with the hypothesis that there are at least two pools of body phosphorus.*

Using hemodialyzers placed in parallel led to higher phosphate clearance and total phosphorus removal. This higher phosphate removal may be related in part to increasing the concentration gradient for transfer out of a second compartment.

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Introduction

During the course of end-stage renal disease, hyperphosphatemia invariably results secondary to the diminished ability of the kidneys to excrete the dietary phosphorus load. Hyperphosphatemia is responsible for secondary hyperparathyroidism through both direct effects on the parathyroid gland and indirect effects of hypocalcemia [1]. Hyperparathyroidism is associated with substantial morbidity secondary to renal osteodystrophy and with the protean effects of parathyroid hormone (PTH) on other end organs [2]. Furthermore, hyperphosphatemia is associated with an increased risk of death in hemodialysis (HD) patients, independent of the level of calcium and PTH [3]. In patients with a serum phosphorus greater than 6.5 mg/dL there is an increased relative risk of death; patients with a serum phosphorus greater than 7.9 mg/dL have a 39% increased rate of death over patients with normal serum phosphorus levels [3].

Given the morbidity and mortality associated with hyperphosphatemia, much effort is expended in attempts to control serum phosphorus levels. These efforts focus on dietary restriction of phosphorus intake, with its attendant risk of protein–calorie malnutrition. If nutrition is to be maintained at adequate levels, then dietary phosphorus binders must be utilized to decrease gastrointestinal absorption of phosphorus. Unfortunately, the most commonly used phosphorus binders rely on calcium-containing compounds, which increase the risk of hypercalcemia and vascular calcifications [4]. Given a daily phosphorus intake of approximately 900 – 1500 mg, with gastrointestinal absorption of 540 – 900 mg per day and HD removal of 300 – 400 mg per day (on average, HD removes 800 – 1000 mg phosphorus per treatment), there is a net gain of 240 – 600 mg phosphorus per day. The only way to decrease this positive balance is to increase dietary phosphorus binding or to increase dialytic removal. Prior studies of dialytic removal of phosphorus have shown that HD is relatively limited in its ability to remove phosphorus [5–7]. This limitation is secondary to multiple pools of phosphorus [8], some

of which are inaccessible to solute removal during dialysis, as well as post-dialytic phosphorus rebound, which can quickly return serum phosphorus levels to pre-dialysis values [9]. Recently, the use of two dialyzers in parallel (DD) has been shown to increase small solute removal [10]. In this study, the use of DD led to an increase in equilibrated Kt/V_{urea} of 16% over a single dialyzer (SD). This increase in clearance is attributed to an increase in the surface area of the dialyzer membrane. The goal of this study was to determine if increased dialysis membrane surface area with the use of high flux, high efficiency hemodialyzers placed in parallel, would result in higher total phosphorus removal compared to that obtained with a single hemodialyzer.

Methods

Patients

Currently in our dialysis unit, patients with weight greater than 80 kg and that do not meet a $Kt/V_{urea} > 1.2$ are placed on DD to meet clearance goals. Given this requirement, patients were not randomized to treatment goals. Five stable patients undergoing chronic HD with DD and 4 stable patients undergoing chronic HD with SD were studied. Demographic data of the study participants are listed in Table I. Exclusion criteria included severe malnourishment [normalized protein catabolic rate (nPCR) < 0.7 and/or albumin < 3.5 g/dL], hospitalization for any cause within the previous 8 weeks, recent change in dialysis prescription, change in dosage of phosphorus binders, and hypotension during dialysis.

The absence of significant access recirculation was confirmed by peripheral blood sampling [11]. Residual renal clearance was not determined in this study and was disregarded for purposes of the study, but all patients had daily urine output less than 200 mL. During the study period there were no changes made in patient medications, including phosphorus-binding agents. Baseline measurement of Kt/V_{urea} (Daugirdas II equation [12]), hematocrit, and nPCR were assessed for the 6 months prior to study entry. The study protocol was reviewed and approved by the University of Virginia Health System Human Investigation Committee, and informed consent was obtained prior to study entry for all patients.

TABLE I Baseline and hemodialysis parameters of enrolled patients. Values are listed as mean ±SD.

	Double dialyzer	*Single dialyzer*
Patients (*n*)	5	4
Age (years)	56±10	52±6
Male/Female	4/1	4/0
Weight[a] (kg)	96±14	62±20
Body surface area[b] (m^2)	2.14±0.13	1.78±0.22
Arteriovenous fistulas (*n*)	1	1
Arteriovenous grafts (*n*)	4	3
Total dialysate collections (*n*)	8	5
Kt/V_{urea}	1.46±0.13	1.35±0.09
Serum phosphorus (mg/dL)	5.9±1.6	5.1±2.3
Serum calcium (mg/dL)	9.8±1.2	9.8±0.6
Dialysis time (minutes)	240	240
Blood flow rate (mL/min)	400	400
Dialysate flow rate (mL/min)	800	800
Ultrafiltration (L)	3.2±1.5	2.6±1.7
Hematocrit (%)	37.4±3.0	36.0±2.1
nPCR (g/kg/day)	1.15±0.17	1.13±0.14

[a] $p = 0.01$.
[b] $p = 0.02$.
nPCR = normalized protein catabolic rate.

Dialysis technique

Hemodialysis was performed using a Fresenius 2008H hemodialysis machine [Fresenius Medical Care of North America (FMC), Lexington, MA, U.S.A.] using bicarbonate-based (35 mmol/L) dialysate. Dialysate calcium concentration was 2.5 mEq/L, and dialysate potassium was 3.0 mEq/L for all patients. All dialysis membranes were polysulfone. Either a single Fresenius F-80 (FMC) or two F-80 dialyzers placed in parallel, as described previously [10], were used. A heat–citric acid method was used to reprocess dialyzers [13].

All patients underwent dialysis for 240 minutes with machine blood flow rates set at 400 mL/minute and dialysate flow rates set at 800 mL/minute. Patients were monitored with blood pressure taken every 15 minutes during treatment, and the dialysis was excluded from analysis if significant hypotensive episodes occurred (defined as blood pressure < 90/60 mmHg or symptoms consistent with hypotension requiring either normal saline or hypertonic saline boluses). Patients were not allowed food or beverages during the dialysis sessions. The required ultrafiltration volumes were determined on the basis of the patient's target weight and interdialytic weight gains.

Study protocol

Patients were studied on the first dialysis day of the week (either Monday or Tuesday). Blood samples were obtained at the beginning of treatment (T0), at 2 hours (T2), and at completion of the dialysis session (T4). Blood samples were analyzed for creatinine, urea, calcium, and phosphorus for each time point. Total dialysate was collected in 55-gallon drums during the HD session. Total dialysate was mixed following completion of the dialysis session and a sample was analyzed for urea, creatinine, phosphorus, and calcium. The total amount of phosphorus (P_T) removed during treatment was calculated from $P_T = V_T \times P_D$, where V_T is the total dialysate volume and P_D is the dialysate phosphorus concentration (this same equation was used to determine the total amounts of urea and creatinine removed). Clearances for phosphorus, urea, and creatinine were determined by dividing the total amount of solute removed in the dialysate by the duration of dialysis (in minutes), and dividing this value by the average of the pre- and post-dialysis concentrations. Kt/V_{urea} was calculated using the second-generation Daugirdas equation [12].

Statistical analysis

All values are reported as mean ± standard deviation (SD). Intergroup comparisons were made using two-tailed t-test for unpaired data and Student's t-test for paired samples. A p value < 0.05 was considered to represent a statistically significant result.

Results

Eight total dialysate collections were obtained from the 5 patients in the DD group, and 5 total dialysate collections were obtained from the 4 patients in the SD group. As prescribed, total dialysis time, and blood and dialysate flow rates were equivalent during all collections (Table I). Ultrafiltration averaged 3.2 ± 1.5 L per session in the DD group, and 2.6 ± 1.7 L per session in the SD group. Serum calcium was equivalent in the DD and SD groups at T0 (9.8 ± 1.2 mg/dL and 9.8 ± 0.6 mg/dL, respectively), while serum phosphorus was higher in the DD group (5.9 ± 1.6 mg/dL) compared to the SD group (5.1 ± 2.3 mg/dL) at T0 (Table I). Kt/V_{urea} was higher in the DD group (1.46 ± 0.13) compared to the SD group (1.35 ± 0.09), although the difference was not statistically significant (p = 0.2) (Table I). The average number of reuses was 6 for the DD group (range 0 – 14) and 4 for the SD group (range 0 – 11).

The total phosphorus removed in the DD group averaged 1594 ± 300 mg, and in the SD group 1108 ± 285 mg (Table II). Phosphorus clearance was 178 ± 32 mL/min in the DD group and 149 ± 38 mL/min in the SD group. The difference in phosphorus clearance between the groups was statistically significant (p = 0.039). Urea clearance was 285 ± 25 mL/min in the DD group and 251 ± 27 mL/min in the SD group; the difference was not statistically significant (p = 0.082). The bulk of phosphorus removal occurred during the first 2 hours of dialysis, as shown in Fig. 1. In the DD group, there was a 58% fall in serum phosphorus levels during the first 2 hours of dialysis, while in the SD group the corresponding fall was 50%. During the last 2 hours of dialysis, serum phosphorus fell by only 18% in the DD group and by 26% in the SD group. The amount of phosphorus removed during the first 2 hours averaged 1.58 mg/dL/hour in the DD group and 1.12 mg/dL/hour in the SD group. During the last 2 hours of dialysis, the rate of phosphorus removal fell to 0.27 mg/dL/hour in the DD group and 0.47 mg/dL/hour in the SD group.

For the 4 patients that had multiple dialysate collections, there was no statistically significant difference in phosphorus clearance with increasing number of dialysis membrane reuses (data not shown).

Discussion

Hyperphosphatemia is the source of much morbidity and mortality in dialysis patients and, as such, great efforts have been made to lower serum phosphorus concentrations through dietary restriction, phosphate binders, and HD. Despite these efforts, nearly 50% of HD patients have serum phosphorus concentrations above 6.5 mg/dL [14]. Several studies have shown that hemodialytic removal of phosphorus averages 800 – 1000 mg per session, a level that is inadequate to compensate for dietary intake of phosphorus [5–7]. This limita-

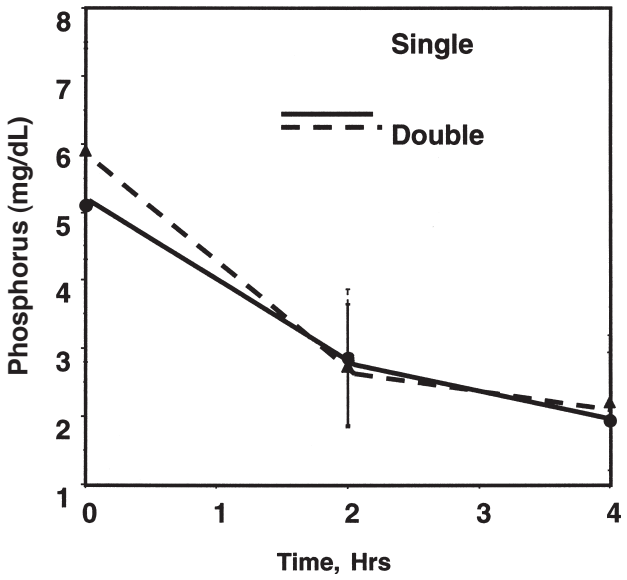

FIGURE 1 Serum phosphorus levels during hemodialysis with single versus double hemodialyzers placed in parallel. Error bars represent the standard deviation of the mean.

TABLE II Clearances and total phosphate removal (mean ±SD).

	Double dialyzer	*Single dialyzer*	p *Value*
Total phosphorus removed (mg)	1594±300	1108±285	0.03
Urea clearance (mL/minute)	285±25	251±27	0.082
Phosphorus clearance (mL/minute)	178±32	149±38	0.039
Reduction in serum phosphorus concentration (%)			
0–2 hours	58	50	
2–4 hours	18	26	
Phosphorus removal (mg/dL/hour)			
0–2 hours	1.58	1.12	
2–4 hours	0.27	0.47	

tion in removal of phosphorus is secondary to the complex kinetic behavior of this solute. A recent kinetic analysis found evidence for up to four phosphate pools [8]. Physiologically, these pools may represent bone, plasma, intracellular, and other unidentified stores. Dialytic removal is largely restricted to the plasma pool and thus is relatively inefficient in decreasing total body phosphorus concentrations. Kinetic studies of phosphorus removal in HD have consistently demonstrated a rapid fall in serum phosphorus early in dialysis, followed by a plateau phase during which phosphate levels decrease minimally or may even increase [15]. The problem is compounded by a significant post-dialytic rebound in phosphorus concentration that can quickly return serum levels to pre-treatment values [9]. Given this complex behavior of phosphorus, it is not surprising that attempts to control serum phosphorus levels have been only partially successful.

The present study evaluated phosphorus clearance when two F-80 hemodialyzers were placed in parallel (DD group) in an attempt increase membrane surface area and Kt/V_{urea}. In this configuration, each dialyzer received 200 mL/min blood flow and 400 mL/min dialysate flow. Despite this fall in blood and dialysate flow rates, Kt/V_{urea} increased in two studies by 16% – 22% [10,16]. These increases in clearance are likely secondary to an increase in membrane surface area. In the present study, phosphorus clearance was 19% higher in the DD group than in the SD group. The total amount of phosphorus removed was 43% higher in the DD group. The higher total phosphorus removal in the DD group was, in part, secondary to a higher pre-dialysis serum phosphorus concentration in this group. This finding is consistent with a prior study by Jindal *et al*. [17] that demonstrated a 30% increase in phosphorus clearance when they switched from a polysulfone membrane with a surface area of 1.3 m^2 to a surface area of 1.9 m^2.

While increased membrane surface area may account for much of the increase in phosphorus clearance in the DD group, the ultrafiltration rate in this group was also higher than that in the SD group. Since convective removal of phosphorus may be important [9], the increased ultrafiltration in the DD group may account for some of the increase in phosphorus clearance, although it seems unlikely that a 0.6 L/day difference in ultrafiltration could account for a significant percentage of the difference in phosphorus removal.

The bulk of phosphorus removal was seen during the first 2 hours of dialysis, after which the rate of phosphorus removal in the DD group was less than that in the SD group. These findings are consistent with other studies of hemodialytic removal of phosphorus, where the bulk of phosphorus removal occurs early in the procedure [8,9]. In addition, a more efficient removal of phosphorus early in the dialysis procedure leads to a slower rate of removal late in dialysis, and a greater post-dialytic rebound in serum phosphorus concentration [9]. This finding is consistent with a simplified model of phosphorus kinetics with rapid clearance of an easily accessible pool of phosphorus, followed by mobilization of phosphorus from other compartments, which equilibrate slowly with the central plasma pool. Despite this complex behavior, increasing the membrane surface area or the convective clearance will increase bulk phosphorus removal.

Although this study did not assess long-term control of serum phosphorus concentrations in patients dialyzed with two parallel dialyzers, a prediction would be that phosphorus levels would be better controlled in the DD group. However, patients in the DD group actually had higher serum phosphorus concentrations despite greater dialytic removal. This may, in large part, be due to the increase in dietary phosphorus intake that occurs with increased dialysis dose. This observation has also been seen in patients switching from three-times weekly to daily HD [18,19]. Another prediction would be that short daily HD treatment would lead to improved phosphorus control, since the bulk of dialytic phosphorus removal occurs during the first 2 hours. Most studies on phosphorus control in short daily HD have not shown superior control; however, two studies reported improved phosphorus control [18,19]. A confounding factor in these studies is that parameters of nutrition and phosphorus intake improve on short daily HD [18,19]. Perhaps using two dialyzers placed in parallel, or a dialyzer with increased surface area, would further improve phosphorus removal in patients on short daily HD.

Hemodialysis with two dialyzers in parallel results in higher clearance of phosphorus, especially during the first 2 hours of dialysis. The higher phosphorus clearance is likely secondary to increased membrane surface area. Utilization of DD could result in up to 1200 mg additional phosphorus removal per week and could decrease reliance on dietary phosphorus binders. The current study is limited by the fact that the sizes of patients in the DD and the SD group were quite different. In patients with refractory hyperphosphatemia, the use of DD may improve control of phosphorus Further studies utilizing a crossover study design will be pursued.

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