The Role of Daily Dialysis in the Control of Hyperphosphatemia

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Abstract

In patients with end-stage renal disease (ESRD), hyperphosphatemia occurs in the vast majority of patients. The numerous clinical sequelae of hyperphosphatemia include secondary hyperparathyroidism and increased risk of cardiovascular death. Chronic hemodialysis as it is currently practiced in the United States does not remove sufficient phosphate to control serum levels within accepted guidelines. The inadequacy of conventional hemodialysis in removing phosphate mandates the use of phosphate binders in virtually all hemodialysis patients. Despite their proven efficacy, these medications fail to control phosphorus in seventy percent of hemodialysis patients. Additionally, these medications may have untoward side effects that must be considered since they are typically intended for lifetime use. Quotidian hemodialysis has in previous uncontrolled studies shown promise in reducing serum phosphorus while at the same time reducing or eliminating the need for phosphate binders. Recent results from our group demonstrate for the first time in a controlled fashion the efficacy of short daily dialysis in controlling serum phosphorus.

Key Words: Phosphorus, phosphorus control, daily hemodialysis, short daily hemodialysis, quotidian hemodialysis, secondary hyperparathyroidism

Cardiovascular disease is present in ESRD patients at rates 10-20 times higher than in the general population and accounts for 50% of deaths among ESRD patients.1-2 Hyperphosphatemia is an emerging risk factor for cardiovascular mortality in the ESRD population.2 The pathogenesis of cardiac disease in the ESRD population is complex but involves the interplay of traditional risk factors along with risk factors that are specific to the dialysis population. The novel risk factors among dialysis patients include hyperphosphatemia, elevated calcium x phosphorus (Ca x P) product, lipoprotein (a), hyperhomocysteinemia, chronic inflammation and left ventricular hypertrophy.3-7 Recently, in a rodent model, hyperphosphatemia has been shown to induce myocardial hypertrophy, independent of effects on hyperparathyroidism or cardiovascular calcification.10 Thus hyperphosphatemia must be viewed in the broad context of a cardiovascular risk factor in addition to its role in initiating secondary hyperparathyroidism.

Conventional hemodialysis does not remove sufficient phosphate to maintain phosphorus balance in the vast majority of hemodialysis patients.2,3,4 A four hour hemodialysis session will clear 34 mmol of phosphate (1054 mg of phosphorus),12,13 which is not sufficient to keep up with the typical phosphorus intake of 800-2000 mg per day (equivalent to 25.8-64.5 mmol of phosphate) in the Western diet. Attempts to enhance phosphate removal through alterations in dialysate composition and dialysis membranes have been largely unsuccessful.14,15

The inability of hemodialysis to adequately remove phosphorus is mainly due to the inaccessibility of phosphate during the treatment. Phosphorus exists mainly in the intracellular compartment. During a hemodialysis session with either a high flux or low flux dialyzer, serum phosphorus decreases rapidly, reaching a hypophosphatemic nadir at about 120 minutes.13,16 There is an immediate post-dialysis rebound in which the serum phosphorus level can even exceed the pre-dialysis value.13,14,16,17 Phosphate efflux into the dialysate is greatest during the first hour of the treatment, corresponding to the time during which serum phosphorus levels are highest.13 Phosphate efflux then falls off, but remains at roughly half the initial value at the end of the treatment despite a stable serum phosphorus levels (Figure 1a). As noted by previous investigators,13,14,16,20 these kinetics suggest a two-phase model of phosphorus removal, the first entailing removal of phosphate from the extracellular fluid compartment, followed by continued dialysis clearance of phosphorus as phosphate is mobilized from a second (intracellular) pool which maintains serum phosphorus levels (Figure 1b).

Thus, the limiting factor in phosphate removal is not the phosphate flux across the dialyzer,15,16 but two other main factors. The first is the rapidity of phosphate removal during the first phase,
or early part of the hemodialysis treatment and the second is the rapidity of intracellular phosphate mobilization during the second phase. The determinant of phosphate removal during this first phase is the serum phosphorus level; this is in fact the most important clinical factor affecting phosphate removal during hemodialysis. Higher serum phosphorus levels allow great phosphate removal during each treatment. Surface area of the dialyzer is also important with larger surface areas removing more, but the flux of the dialyzer is not important. The determinant of phosphate removal during the second phase of hemodialysis is the rapidity of phosphate mobilization from body pools (Figure 1a). It has been shown that hemodiafiltration can increase phosphate mobilization from the tissues by increasing the post-dialytic phosphate rebound. Thus hemodiafiltration acutely increases pre-dialytic phosphorus levels, but over three months decreases serum phosphorus. The proposed mechanism for the increased phosphate removal is the convective removal of this solute during hemodiafiltration. Unfortunately, hemodiafiltration is a modality not readily available to ESRD patients in the United States.

Since conventional 3 times per week hemodialysis is inadequate to maintain phosphate balance at acceptable serum levels of phosphorus, the use of phosphate binders is mandatory to minimize phosphorus absorption from the diet. Currently two options exist in the United States to bind intestinal phosphate on a chronic, long term basis: calcium-based binders and sevelamer. Calcium acetate and calcium carbonate are effective in reducing serum phosphorus levels in hemodialysis patients and in reducing secondary hyperparathyroidism. However, concerns have been raised about the safety of the long term use of calcium based binders because of the potential for the chronic calcium load to induce cardiovascular calcification, especially in the context of the use of vitamin D analogues. Sevelamer hydrochloride, a

Table 1. Summary of Daily Dialysis Studies

<table>
<thead>
<tr>
<th>Author (Ref)</th>
<th>No. of subjects</th>
<th>Dialysis Modality</th>
<th>Prescription / (Duration)</th>
<th>Phosphorus Control</th>
<th>Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kooistra [18]</td>
<td>13</td>
<td>Daily home hemodialysis</td>
<td>6 times weekly (6 months)</td>
<td>Decrease dose of P binders</td>
<td>Decreased blood pressure in hypertensive patients</td>
</tr>
<tr>
<td>Uldall [17]</td>
<td>5</td>
<td>Nocturnal hemodialysis</td>
<td>5-7 nights/wk, 8 hrs/night, (6-16 months)</td>
<td>Discontinue P binder use</td>
<td>Increased dietary protein intake</td>
</tr>
<tr>
<td>Mucsi [20]</td>
<td>7</td>
<td>Nocturnal hemodialysis</td>
<td>6 nights/wk, 8 hrs/night, (5 months)</td>
<td>Discontinue P binder use</td>
<td>Increased dietary protein intake</td>
</tr>
<tr>
<td>Lindsay [21]</td>
<td>12</td>
<td>Nocturnal hemodialysis</td>
<td>5-6 nights/wk, 6-8 hrs/night, (5-36 months)</td>
<td>Decreased use of P binder, Decreased Ca x P product</td>
<td>Improved blood pressure control, Improved QOL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short daily hemodialysis</td>
<td>5-6 days/wk, 1.5-2.5 hrs/day, (5-36 months)</td>
<td>Decreased Ca x P product</td>
<td>Improved blood pressure control, Improved QOL</td>
</tr>
<tr>
<td>Mizani [23]</td>
<td>51</td>
<td>Conventional hemodialysis</td>
<td>3 days/wk 4 hrs/day (One year)</td>
<td>No change in phosphorus, continued use of phosphate binders</td>
<td>Decreased iPTH</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Short daily hemodialysis</td>
<td>6 days/wk 3 hrs/day (One year)</td>
<td>Decreased serum phosphorus, 73% patients discontinue the use of phosphate binders at 12 months</td>
<td>Decreased iPTH</td>
</tr>
</tbody>
</table>
quaternary amine anion exchange resin that binds phosphate ions and releases hydrochloric acid is an alternative phosphate binder that is neither aluminum nor calcium based. This agent is also effective in reducing phosphorus and reducing hyperparathyroidism and does not expose the patient to a calcium load. Because of its mechanism of action, sevelamer can lead to an acid load and in animal studies has been associated with acidosis. Nonetheless, despite use of these phosphate binders, dietary phosphorus restriction, and conventional hemodialysis, seventy percent of patients on hemodialysis fail to achieve goals for serum phosphorus and Ca x P product recommended in the K/DOQI guidelines.

In order to control serum phosphorus more effectively in our ESRD population as a whole, dialytic removal of phosphorus must be improved. Given the kinetics of phosphate removal during dialysis, it is clear that the time of dialysis must be increased in order to achieve better phosphate removal with hemodialysis. The HEMO study demonstrated that increased dose of dialysis, without much increase in time of dialysis did not favorably affect mortality. Despite these findings, several groups have found beneficial effects on cardiovascular risk factors; blood pressure control, improved anemia by reducing erythropoietin requirements, and regression of left ventricular hypertrophy with the use of quotidian dialysis. Additionally, control of serum phosphorus is reportedly improved with the use of either daily or nocturnal dialysis. In our study, instead of dividing the twelve hour weekly time over six two-hour sessions, we increased both the total time and the frequency of hemodialysis (six times per week for three hours) in order to maximize phosphate removal. Assuming a low phosphorus intake of 900 mg per day of phosphorus (equivalent to 29 mmol of phosphate), and phosphorus kinetics shown in figure 1a, conventional hemodialysis is woefully inadequate at achieving phosphorus balance, while short daily hemodialysis comes much closer to this goal without the use of phosphate binders (Figures 2a and 2b).

There are only four studies of quotidian dialysis that address the issue of phosphorus control. The summary of our review of the literature is presented (Table 1). A universal finding in these studies is either a decrease in requirement for phosphate binders or complete cessation of these agents. Additionally, concurrent increases in protein intake have been reported in two of these studies. Lindsay and colleagues reported a significant decrease in Ca x P product using a short daily hemodialysis regimen (1.5 - 2.5 hours a day, six days a week), and using nocturnal hemodialysis. In the nocturnal hemodialysis group this was achieved with a reduction in the use of phosphate binders.

Our study is the first to assess, in a large group of patients, the efficacy of short daily hemodialysis in reducing serum phosphorus in a controlled manner. Our study employed a protocol

Table 2. The San Antonio Prospective Study on Daily Dialysis

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
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<tbody>
<tr>
<td><strong>Conventional Hemodialysis, CHD (N=51)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>9.0 ± 0.70</td>
<td>8.8 ± 0.55</td>
<td>8.9 ± 0.65</td>
</tr>
<tr>
<td>P (mg/dL)</td>
<td>5.0 ± 1.49</td>
<td>4.9 ± 1.12</td>
<td>5.1 ± 1.14</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>717 ± 361</td>
<td>255 ± 182 *</td>
<td>428 ± 312 *</td>
</tr>
<tr>
<td><strong>Short Daily Hemodialysis, SDHD (N=26)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>8.4 ± 1.26</td>
<td>9.0 ± 0.66 *</td>
<td>8.9 ± 0.74 *</td>
</tr>
<tr>
<td>P (mg/dL)</td>
<td>6.3 ± 2.57</td>
<td>4.6 ± 1.06 *</td>
<td>4.0 ± 1.19 *</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>690 ± 596</td>
<td>337 ± 255 *</td>
<td>312 ± 193 *</td>
</tr>
</tbody>
</table>

Adapted from Mizani and Ayus (ref 36)
73% of SDHD patients discontinued phosphate binders at 12 months.

* P < 0.05 vs. baseline (intra-group comparison)
†P < 0.05 SDHD vs. CHD (inter-group comparison)
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that called for three hours of hemodialysis six times per week. The conventional hemodialysis group was treated for four hours three times per week. In addition to delivering a 60% greater weekly Kt/V, this short daily hemodialysis (SDHD) regimen maximizes phosphate removal, by increasing the total dialysis time. In our study, 77 hemodialysis patients matched for age, sex and comorbidities were treated with either conventional thrice-weekly dialysis (n = 51) or were treated with short daily hemodialysis (n = 26). Table 2 summarizes the observations from this study. A significant reduction in PTH levels of 55% and 40% was seen in the SDHD and conventional dialysis groups, respectively. A significant decrease in serum phosphorus levels was seen in the patient group treated with SDHD (6.3 + 2.57 mg/dL at baseline, 4.61 + 0.6 mg/dL at 6 months of treatment, and 4.0 + 1.19 mg/dL at 12 months of dialysis treatment, p<0.004) that was not seen in the patients on conventional hemodialysis. This statistically significant reduction in serum phosphorus occurred despite the withdrawal of phosphate binders in 73% of the SDHD group while the phosphate binder requirements were unchanged in the control group. To our knowledge, this is the first controlled study to demonstrate effective control of serum phosphorus level using short daily hemodialysis in a large group of patients with ESRD.

Figure 1b. Phosphate removal during hemodialysis involves two phases. The figure depicts two phases of phosphate removal. At the start of the treatment, the rate limiting step is the rapidity of phosphate removal from the extracellular fluid as depicted by the large arrow. The second phase occurs when the serum phosphorus level has reached a nadir and the removal is limited by phosphate mobilization from the tissues.

Figure 2a. Conventional hemodialysis alone leads to significantly positive phosphorus balance. Using the phosphate removal from a four hour hemodialysis treatment shown in figure 1a, and assuming a phosphorus intake of 900 mg (equivalent to 29 mmol of phosphate), the predicted phosphate balance using conventional hemodialysis over the week is shown.

Figure 2b. Short daily hemodialysis alone is close to achieving phosphate balance. Using the phosphate removal from a three hour hemodialysis treatment shown in figure 1a, and assuming a phosphorus intake of 900 mg (equivalent to 29 mmol of phosphate), the predicted phosphate balance using short daily hemodialysis over the week is shown.
In conclusion, uncontrolled hyperphosphatemia is a serious shortcoming in the delivery of hemodialysis in the United States. In addition to exposing patients to the morbidity of secondary hyperparathyroidism, it is increasingly clear that hyperphosphatemia is a serious cardiac risk factor. Conventional hemodialysis does not remove adequate phosphorus to maintain phosphorus balance without the use of phosphate binders. Even the addition of these medications is not sufficient to attain KDOQI guidelines for control of phosphorus and Ca x P product in the majority of patients and all phosphate binders have potential side effects which must be considered. Previous investigators have shown that daily hemodialysis is efficacious in controlling serum phosphorus.32-35 Our group has shown for the first time in a large group of patients, in a controlled manner, that short daily hemodialysis can control hyperphosphatemia while nearly eliminating the need for phosphate binders.36 In our opinion, daily hemodialysis is the best treatment to control hyperphosphatemia and ameliorate both the metabolic and cardiovascular complications of this disorder.

References

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