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VITAMIN D IN PATIENTS WITH RENAL FAILURE: A SUMMARY OF OBSERVATIONAL MORTALITY STUDIES AND STEPS MOVING FORWARD

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Abstract

Although approximately half of patients undergoing hemodialysis receive activated forms of vitamin D, the primary reason to initiate this therapy has rested solely on the management of secondary hyperparathyroidism. Secondary hyperparathyroidism is likely one of several consequences of vitamin D deficiency, however, and only now have other consequences of vitamin D deficiency emerged. Although previously viewed as a contributor to hypercalcemia and hyperphosphatemia, recent studies suggest vitamin D may improve cardiovascular structure and function, improve vascular compliance, and reduce pro-inflammatory cytokines, all of which may contribute to the improved survival observed in retrospective studies examining the outcome of patient treated with activated vitamin D compared to those who were not. The current review examines two recent large-scale studies of hemodialysis patients: one that demonstrated a survival advantage of paricalcitol over calcitriol and a second that demonstrated a significant survival advantage of any intravenous vitamin D formulation versus none. In both studies, the findings were independent of mineral and parathyroid hormone levels, suggesting “non-traditional” actions of vitamin D contributed to the observed survival advantage. Potential steps moving forward in light of these studies are subsequently discussed.

PARICALCITOL AND CALCITRIOL AND HEMODIALYSIS SURVIVAL

Although several studies have implicated disorders of mineral metabolism in the excessive risk of cardiovascular mortality in ESRD patients, few if any of these studies examined the role of vitamin D and its contribution to outcomes.[4,10,11,13] Given these observations and the differential effects of paricalcitol and calcitriol on PTH suppression and their relative incidence of hypercalcemia and hyperphosphatemia,[15,16,21] we first studied the survival of patients treated with either one of two injectable vitamin D preparations that were used widely between 1999 and 2001. Our motivation to perform this study was to examine survival according to different formulations of activated vitamin D, and the study was not supported by industry. In this historical cohort study, we examined 67,399 hemodialysis patients who received treatment with intravenous paricalcitol (n=29,021) or calcitriol (38,378) between January 1, 1999 and December 31, 2001 at any one of the over 1,000 Fresenius Medical Care dialysis centers in the United States. The primary analysis examined the survival of patients who were treated exclusively with the same vitamin D formulation throughout the study period. In a secondary analysis, we examined the subsequent survival of patients who switched from either vitamin D formulation to the other.

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During the 36-month study period, the mortality rate in the paricalcitol group was 3,417 per 19,031 person-years of observation (0.18 per person-year), compared to 6,805 deaths per 30,471 person-years (0.223 per person-year) in the calcitriol group (relative risk ratio 0.80; 95% confidence interval, 0.77 to 0.84; $P < 0.001$). In absolute terms, the 36-month survival difference was 59% in the paricalcitol group compared with 51% in the calcitriol group, or an 8% absolute difference in survival. After adjusting for age, gender, race, etiology of renal failure, dialysis duration, diabetes, access type, dialysis adequacy, and laboratory values (calcium, phosphate, PTH, albumin, hemoglobin, A1C, ferritin, iron saturation, bicarbonate) using Cox proportional-hazards models, there remained a 16% survival advantage associated with paricalcitol treatment (95% confidence interval, 10% to 21%; $P < 0.001$). In the secondary analysis, the 14,862 patients who switched from calcitriol to paricalcitol demonstrated a significant survival advantage compared to the 1,621 patients who switched from paricalcitol to calcitriol (subsequent 2-year survival 73% versus 64%; $P = 0.04$). Of course, all patients who switched had to be alive up until the time they switched, but after switching, their subsequent survival mimicked the original survival curves observed in the primary analysis. This latter “switch” analysis added significant support to the primary analyses.

Stratified analyses were performed to assess for effect modification and to insure that one specific stratum did not skew the data. Paricalcitol treated patients demonstrated a significant survival advantage in 28 of the 42 strata examined (by age, gender, race, diabetes, etiology of ESRD, access type, duration of dialysis prior to starting vitamin D therapy, and calcium, phosphorus, and parathyroid hormone levels at the start of therapy) and in no stratum was calcitriol superior. In addition, in specific strata such as in African Americans, the survival advantage was greater than that observed in the summary analysis. While increases in the baseline calcium, phosphorus, and parathyroid hormone levels were independently associated with increased mortality as has been shown in previous studies, the risk of death for the paricalcitol group was lower than calcitriol in all calcium, phosphorus, and parathyroid hormone subgroups. The increase in calcium and phosphate levels from the initiation of treatment through the follow-up period was greater in calcitriol treated patients compared to paricalcitol. Review of causes of death revealed that paricalcitol therapy was associated with a decreased risk of cardiovascular, infectious and other causes of death.

The results of this historical cohort study suggested that treatment with paricalcitol appears to be associated with a significant survival advantage compared to treatment with calcitriol. Although all data for this study were collected prospectively and no additional data were abstracted from records (hence minimizing bias), the analysis was performed retrospectively and only a prospective, randomized controlled study would minimize bias and confounding and allow definitive conclusions to be drawn.

Indeed, while the non-mineral/PTH effects of calcitriol are well known, growing literature on the non-mineral/PTH effects of paricalcitol and other analogs supports alternative mechanisms that may explain the survival differences. In this study we did not include a group that did not receive activated vitamin D, since both groups received either calcitriol or paricalcitol. Several of the analyses (e.g., a survival benefit apparent irrespective of baseline serum levels of calcium, phosphorus, or PTH), however, suggested there may be a benefit of receiving any form of activated vitamin D. Alternatively, it would be entirely possible that therapy with activated vitamin D may confer a survival disadvantage given its potential to raise serum calcium and phosphorus levels.[14,19]

THERAPY WITH ANY ACTIVATED VITAMIN D AND HEMODIALYSIS SURVIVAL

We next tested the hypothesis that incident chronic hemodialysis patients who receive any injectable vitamin D formulation have a survival advantage over comparable patients who receive no injectable vitamin D. Once again, this study was not sponsored by industry. In our previous study, clinicians started one or the other form of injectable vitamin D, and thus baseline characteristics in the two groups were similar given that clinicians likely used similar criteria to initiate therapy. For this next study, however, we examined a group that never received injectable vitamin D, hence we expected important differences in the two groups. We performed a historical cohort study of 51,037 new chronic hemodialysis patients living throughout the U.S.[22] All patients were new to chronic hemodialysis (unlike the first study which examined prevalent patients), and 2-year survival was the primary outcome. At baseline, compared to patients who did not receive injectable vitamin D (n=13,864), patients who initiated treatment with any injectable vitamin D (n= 37,173) had clinically comparable levels of serum calcium and phosphorus, however, serum levels of parathyroid hormone (354 ± 336 vs. 179 ± 217 pg/ml, $p < 0.01$) differed. Despite baseline differences, two-year survival was 75.6% in the group who received injectable vitamin D, compared with 58.7% in the group that never did (log rank $P < 0.001$). Corresponding mortality rates were 13.8 per 100 person-years and 28.6 per 100 person years, respectively ($P < 0.001$). Following adjustment for potential confounders using Cox regression analysis, patients who received any form of injectable vitamin D had a 20% (HR 0.80, 95% CI 0.76-0.83) lower mortality compared to patients who never received injectable vitamin D.

We performed a variety of sensitivity analyses to assess the robustness of these results. For example, given marked differences in serum PTH between patients who received activated vitamin D and those who did not, we adjusted for the propensity of receiving activated vitamin D therapy using a sophisticated technique called marginal structural models.[6] Even when employing this technique – which not only provided additional adjustment for baseline covariates but also updated serum levels of calcium, phosphorus, and PTH each month in all patients – the benefits of activated vitamin D remained present. The point estimate (~ 0.80) was similar using each method (Cox proportional hazards models or Marginal Structural Models), and the benefit was apparent in 48 of 49 strata examined. This study, similar to the one described above, was still subject to confounding and bias, and only a prospective randomized trial could definitively answer the question of “*any vs. none.*”

STEPS MOVING FORWARD

Despite these large studies, a number of questions remain. First, we must acknowledge that these studies were observational, and hence subject to bias and confounding. One plausible next step is to perform a large randomized control trial to address the “*any vs. none*” question. Such a study, however, will require several thousand individuals, will take several years to enroll and complete, and will be costly. Given the track record in dialysis trials in which all interventions to date have been shown to be either of no benefit or harmful,[3,8,23] proceeding into such a trial will not occur immediately. Nevertheless, while such a study is being planned, other studies can bring us closer to the truth. For example, testing whether these results hold true when tested prospectively, and in other populations, will be important. Additionally, it is unclear whether therapy with activated vitamin D should be based on serum levels of PTH, or if therapy with vitamin D should be based on correcting a deficiency of either the nutritional or hormonal forms of vitamin D. Treating a nutritional or hormonal deficiency by replacing with each is not an unreasonable proposition. Finally, the mechanisms potentially leading to a survival benefit must be explored, and a variety of investigators have recently highlighted the potential cardiovascular benefits of activated vitamin D therapy.[1,2,25] The vitamin D

receptor knockout model develops left ventricular hypertrophy and hypertension,[24] both common findings in patients with renal failure.[10] We and others are currently examining the effect of activated vitamin D on animal models that develop left ventricular hypertrophy, diastolic dysfunction, and congestive heart failure (unpublished), and simultaneously planning human studies with similar endpoints. Animal and human studies suggest activated vitamin D can suppress pro-inflammatory cytokines [2,17,25] or improve the ability to fight infection, [12] and our group and others are currently examining these surrogates in larger human studies. A variety of investigators have also focused on the improved metabolic profile associated with activated vitamin D therapy,[18] and these mechanisms may also be relevant in patients with renal failure. Therefore, the next wave of studies should focus on specific targets linking renal disease, cardiovascular disease, and mortality, obtaining clues from biology, animal, and human studies, and vigorously testing these mechanisms in “pilot” human studies as larger clinical trials are planned.

CONCLUSION

While the nephrology community has largely focused on the ability of vitamin D to lower serum levels of parathyroid hormone,[9] the vitamin D receptor is ubiquitous, and activation of this receptor has widespread effects.[5] The biology of vitamin D is tightly interwoven with the biology of serum calcium, phosphorus, and parathyroid hormone, and thus separating out the independent effects of one from the other has been a challenge. Nonetheless, previous observational studies implicating alterations of serum calcium, phosphorus, or parathyroid hormone as independent factors associated with mortality among chronic hemodialysis patients did not account for whether patients were receiving injectable vitamin D, and whether vitamin D administration itself altered these associations. Furthermore, these past studies have formed the basis for several guidelines to manage chronic dialysis patients. In contrast, the potential adverse consequences of vitamin D administration have been highlighted by.[7,14,19,20] A variety of studies are now emerging to suggest therapy with vitamin D may have additional benefits, well beyond control of serum levels of parathyroid hormone.

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