Efficacy of Cholecalciferol In The Management Of Secondary Hyperparathyroidism In Hemodialysis Patients.

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Abstract:

Introduction:
Conventionally, secondary hyperparathyroidism (SHPT) has always been treated with active vitamin D analogues like calcitriol or calcidiol. The role of native vitamin D in end stage renal disease patients (ESRD) patients has always been questioned

The aim of our study is to evaluate the role of native vitamin D in the form of cholecalciferol in the management of secondary hyperparathyroidism in patients on maintenance hemodialysis. This is the first study to assess the role of cholecalciferol as a sole therapy in the management of SHPT in hemodialysis patients with concomitant vitamin D deficiency/insufficiency.

METHODS: Forty-two maintenance hemodialysis patients were included with serum PTH > 300ng/L and vitamin D3 levels < 30ng/ml. Patients were followed for 3 months. Patients with vitamin D deficiency (vit D3 levels 5-15 ng/ml) were treated with Inj. Vitamin D3 600,000 I.U. monthly for 3 months. Patients with vitamin D insufficiency (16-30 ng/ml) were treated with 200,000 I.U. monthly for 3 months.

RESULTS: Total 42 patients were taken with 16 male and 26 female patients. After treating patients with cholecalciferol, serum PTH levels improved significantly, with mean pre-treatment levels of 591.50±180.09, which had decreased to a mean post-treatment level of 317.80±199.05. Serum Vitamin D levels also improved significantly, with mean pre-treatment levels of 10.47±5.84, which increased to a mean post-treatment level of 33.33±15.31.Patients treated with cholecalciferol had no significant change in calcium and phosphorous levels.

CONCLUSION: Native vitamin D in the form of cholecalciferol appears to be safe, effective and is inexpensive in the treatment of secondary hyperparathyroidism in patients on maintenance hemodialysis with no adverse effects.

Keywords: *Cholecalciferol, Parathyroid Hormone, Vitamin D, hemodialysis, Secondary Hyperparathyroidism.*

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Introduction:

Vitamin D, one of the fat-soluble vitamins has always been considered as a precursor of endocrine agent, regulating calcium and bone mineral homeostasis until the end of the 20th century. However the past decade has seen a blossoming of data showing that vitamin D has an autocrine action (that is, the activity of vitamin D arises from 1-25 Vit D, synthesized within those cells) and /or a paracrine action (that is, 1-25 Vit D, synthesized in one cell type and acts on adjacent cells).[1] Many tissues like pancreas, colon, skin, breast, prostate, macrophages and cells of vasculature and cerebellum; not only express Vitamin D receptor but also possess 1-alpha hydroxylase and are therefore capable of production of 1, 25 dihydroxy-vitamin D, which may act locally.[2] This may indicate an autocrine /paracrine function of this enzyme in the control of cell proliferation and differentiation. Patients with stage 5 CKD are at high risk for deficiency in the storage form of vitamin D due to variety of factors including poor dietary intake, reduced sunlight exposure, and decreased skin synthesis of pre vitamin D.[3] Recently studies have been done showing that repletion of native vitamin D stores in the form of native vitamin D led to improved cardiac function, increased immunity, decreased inflammation with improved hematocrit. The data regarding its role in the management of SHPT is very low. The Kidney Disease Outcome Quality Initiative (KDOQI) guidelines also recommend the use of native vitamin D in early stages of CKD in the management of secondary hyperparathyroidism with concomitant vitamin D deficiency/insufficiency.[4] However, there is no study regarding its role as a main therapy in the management of SHPT in end stage renal disease patients. This is the first study to evaluate its role as a sole therapy in the management of SHPT.

Patients and Methods:
This was a prospective study. The study was designed for a period of 6 months. But the target levels of either PTH or vitamin D were achieved in 3 months. The study included 42 patients. All patients included in the study had serum PTH > 300 ng/L and Vitamin D3 levels < 30 ng/ml. Serum PTH levels were measured with electrochemiluminescence immunoassay (ECLIA). Vitamin D levels were measured with electrochemiluminescence immunoassay (ECLIA). Patients were followed for 3 months. Patients with vitamin D deficiency (vit D3 levels 5-15 ng/ml) were administered Inj. Vitamin D3 600,000 I.U. monthly for 3 months. Patients with vitamin D insufficiency (16-30 ng/ml) were administered 200,000 I.U. monthly for 3 months. Serum concentration of parathyroid hormone (PTH) and vitamin D3 were followed at baseline and at 3 months. Serum Phosphorus (PO4) and Serum calcium (Ca) were monitored monthly. Calcium levels in dialysate was 1.5mmol/L in all patients.
S*tatistical analysis:* Data are reported as the mean+- SD. The paired sample *t*-test was used to compare the values. A P-value of <.05 was considered to be statistically significant. Statistical analyses were performed using the SPSS version 15.

Inclusion criteria:

Patients on maintenance hemodialysis for >6 months

- Age 18-70 years

Exclusion Criteria:

Patients with:

- Corrected Serum Calcium >10 mg/dl
- Serum Phosphorus >5.8 mg/dl
- Severe hyperparathyroidism SPTH >800 pg/ml
- Calciphylaxis
- Liver Disease
- Sarcoidosis

Results:
Total 42 patients were taken with 16 male and 26 female patients. Results were interpreted by applying paired t-test, from perspective of patient age being <=45 or >45, gender, patient being diabetic or non-diabetic and vitamin D3 levels being <=15ng/ml or >15 ng/ml. All the patients had PTH levels > 300 ng/L before the treatment with cholecalciferol. After treating patients with cholecalciferol serum PTH levels improved significantly, with mean pre-treatment levels of 591.50±180.09, which had decreased to a mean post-treatment level of 317.80±199.05. Serum Vitamin D levels also improved significantly, with mean pre-treatment levels of 10.47±5.84,

which had increased to a mean post-treatment level of 33.33±15.31. Patients treated with cholecalciferol had no significant change in calcium and phosphorous levels.

Table-1: Demographic characteristics of 42 patients on maintenance hemodialysis

	n(%)
Age(years)°	55.26±9.66
Dx Duration(months)°	16.61±16.22
Gender	
Male	16(38.1)
Female	26(61.9)
Diabetes Mellitus	
Yes	19(45.2)
No	23(54.8)

Table-2: laboratory parameters pre and post cholecalciferol administration.

	Pre Treatment Mean±SD	**Post Treatment** Mean±SD	**P-Value**
Serum PTH	591.50±180.09	317.80±199.05	0.000
Serum Ca	8.72±0.56	8.81±0.50	0.263
Serum Po4	4.67±0.72	4.76±0.58	0.378
Vitamin D3	10.47±5.84	33.33±15.31	0.000

Paired t-test was applied.

P-value≤0.05, considered as significant.

Discussion:

The novel aspect of our study is significant reduction of serum PTH levels with cholecalceferol monotherapy. The result was more remarkable in patients with vitamin D deficiency i.e. when levels were < 15ng/ml as compared to patients with vitamin D insufficiency (levels between 15 ng/ml-30 ng/ml).

The kidneys of patients with end stage renal disease are unable to produce 1,25 (OH)2 D due to impaired 1α hydroxylation.[5,6] Studies have also shown the role of phosphaturic bone protein fibroblast growth factor 23 which is found to be increased in patients with CKD and is associated with impaired renal 1α hydroxylation.[7,8] However, extrarenal presence of 1 alpha hydroxylase enzyme in parathyroid, adrenals, pancreas and brain tissue has been reported which remain functional in CKD patients.[9,10] Various studies have found strong association between decreased vitamin D levels and many diseases like autoimmune disorders, malignancies, tuberculosis and cardiovascular disorders. This associative connection led to the concept that vitamin D has important autocrine and paracrine effects along with well-established endocrine effects. Local activation of calcidiol into calcitriol plays important role in the regulation of cellular proliferation and differentiation of epithelial cells around the body, regulation of anti-microbial activity of monocytes and control of the immune system.[11-13]

Table-3: Overall mean comparison pre and post cholecalciferol administration according to vitamin D3 level

		Pre Treatment Mean±SD	Post Treatment Mean±SD	P-Value
Vitamin D≤15	**Serum PTH**	**622.62±31.36**	**293.90±194.59**	**0.000**
	Serum Ca	8.68±0.53	8.76±0.48	0.345
	Serum PO4	4.70±0.76	4.84±0.57	0.305
	Vitamin D3	7.68±2.66	28.96±12.80	0.000
Vitamin D>15	**Serum PTH**	**491.90±157.61**	**394.30±203.82**	**0.094**
	Serum Ca	8.87±0.64	8.98±0.61	0.577
	Serum PO4	4.57±0.59	4.53±0.58	0.795
	Vitamin D3	19.40±3.83	47.30±14.81	0.000

Paired t-test was applied.
P-value≤0.05, considered as significant.

The new paradigm shift of the actions of vitamin D altered view of many towards treatment regimen of renal disease.
The evaluation of 25 (OH) D levels in patients with chronic kidney disease has already been recommended by the Kidney Diseases Outcomes Quality Initiative (KDOQI) guidelines and is in accordance with the general population.[4] Keeping in view of the easy availability, cost effectiveness and compliance, we preferred monthly administration over weekly administration. Our data suggests that monthly administration of cholecalciferol decreases serum PTH levels significantly with no evident toxicity. A significant increase in the 25(OH)D and as well as in 1,25 (OH)2 D after cholecalciferol administration has been reported earlier.[14,15] Although activated vitamin D analogues are recommended for activation of vitamin D receptor and thus control of SHPT. But keeping in view the additional health benefits of inactive vitamin D, it is important to know what should be the best strategy to activate it, and should inactive or activated vitamin D be used? [16,17]
Our monthly vitamin D regimen has the advantage of compliance and low cost. The cost of cholecalciferol 600,000 IU in Pakistan is 350 Rs (US$ 2.26) per vial and the cost of 200, 000 i.u. is 150 Rs. (US$ 0.96) which is cheaper than the cost of oral cholecalciferol capsules and other active vitamin D analogues.

While our understanding of vitamin D metabolism continues to expand, many important aspects of vitamin D levels and treatment regimen need to be defined.
Our study has several limitations. We did not address seasonal variations in serum 25-(OH)D, well known in the healthy population. However, it may be much less variable in hemodialysis patients with their considerable different lifestyle. Moreover, seasonal variations are not very remarkable due to tropical climate of our country. The study group was very small and we did not have a control group. But this work can be considered as a pilot and proof-of-concept study.

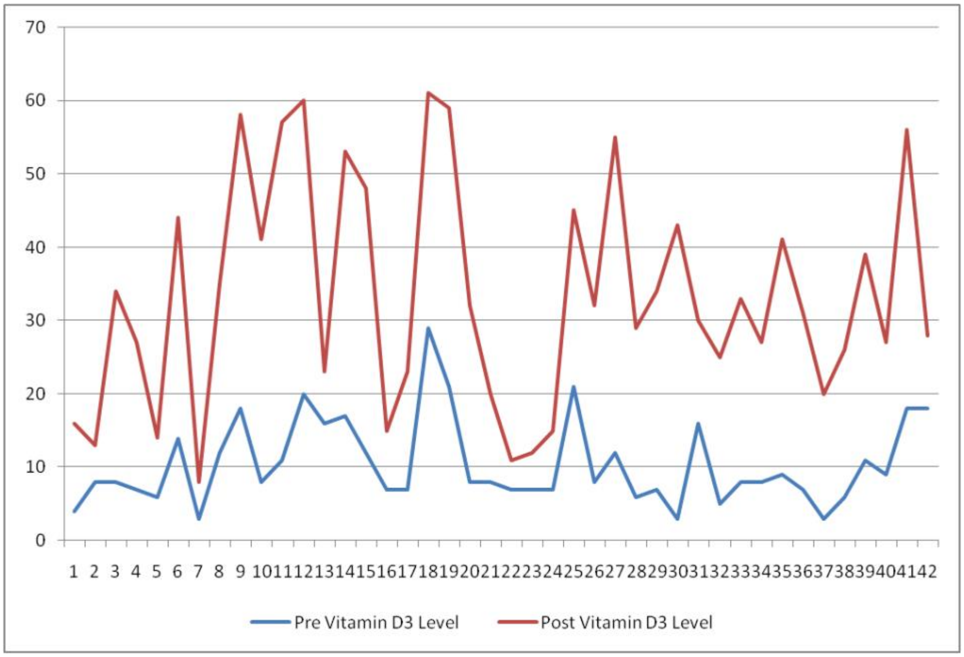

Figure-1: Line chart presenting pattern of vitamin D level pre and post treatment with Cholecalciferol

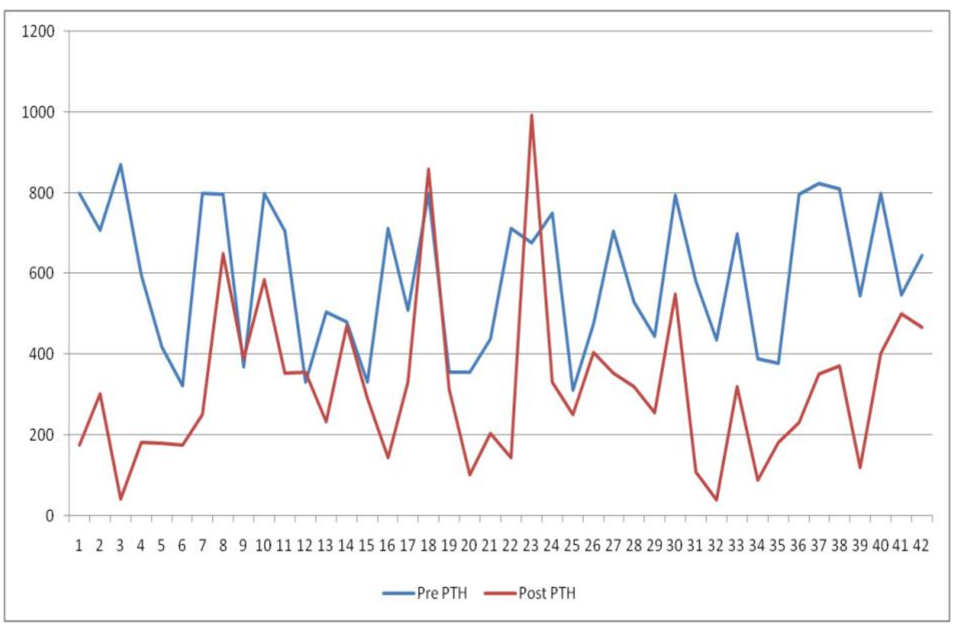

Figure-2: Line chart presenting pattern of PTH level pre and post treatment with Cholecalciferol in 42 hemodialysis patients.

Conclusion:
Monthly administration of cholecalciferol administration appears to be simple, effective and inexpensive with no adverse effects in the management of SHPT in ESRD patients on hemodialysis. However more randomized, controlled and large sample size studies need to be undertaken with longer follow up to better define the role of cholecalciferol for treating SHPT in ESRD patients

Conflict of Interest: None

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