ORIGINAL ARTICLE

IMPACT OF PARICALCITROL ON INFLAMMATORY AND ANAEMIA MARKERS IN DIALYSIS PATIENTS

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Background: The role of Vitamin D in calcium and phosphate homeostasis is renowned. The effects of vitamin D on bone metabolism have been established for long. We planned to see the effects of vitamin D analogue paricalcitrol as on mineral bone disorder in chronic kidney disease. (CKD MBD) parameters and markers of anaemia and inflammation. **Method:** This prospective and observational study was done at King Fahd Hospital, Medina, Saudi Arabia for 3 months from Jan to Apr 2017. Two hundred and ten (210) patients fulfilled the eligibility criteria. Paricalcitrol was given at a dose of 0.04 µg/Kg 3 times a week and parathyroid (PTH) was monitored for 3 months and subsequently the dose was titrated to the PTH levels. We looked at the relationship between paricalcitrol and anaemia markers, inflammatory markers, and erythropoietic stimulating agent dose. **Results:** Two hundred and ten (210) patients were studied, mean age was 50 years, 55% were males; 120 were excluded who had vitamin D level in the normal range, who received vitamin D in the recent past, with phosphate levels >2 and calcium levels >2.55 mmol/L, on calcimimmetics, parathyroidectomy cases, and patients with active infection or malignancy. Parathyroid hormone (PTH) fell significantly -166.4 (95% CI -290, -42.5, $p<0.05$), Transferrin saturation improved significantly (4.4% 95% CI 1.6, 7.2 $p=0.003$). CRP fell significantly ($p<0.01$). However, Hb or ESA requirement did not reach statistical significance. **Conclusion:** Paricalcitrol treatment is associated with improvement in secondary hyperparathyroidism in haemodialysis population. There is a signal towards improvement in markers of inflammation and anaemia but a larger Randomised Control Trial (RCT) is needed to be done.

Keywords: Vitamin D analogue, CKD, MBD, anaemia, inflammatory markers, paricalcitrol

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INTRODUCTION

Chronic Kidney Disease (CKD) has low serum 25-hydroxy vitamin D which then leads to production of calcitrol.[1] The prevalence of vitamin D deficiency varies from study to study but roughly is in the range of 70 to 80 percent.[2] Actions of vitamin D are beyond the calcium-phosphorus-PTH axis. These actions are due to renal and extra-renal 1-alpha-hydroxylase activity, and are through vitamin D receptor on immune system cells and various tissues of the body including pancreas, kidney, breast intestine and colon.[2] The renal protective effects of vitamin D are due to diverse causes.[3] It has been shown to prevent the progression of CKD[4], in addition deficiency of vitamin D has been shown with increased mortality in CKD population.[5]

Some systemic inflammatory processes have been associated with vitamin D[6,7]; studies have shown a link between vitamin D deficiency and markers of inflammation[8,9]. In one trial replenishment of vitamin D was found to decrease markers of inflammation.[10] The studies looking at the relationship between vitamin D and inflammation have excluded patients with CKD. The aim of this prospective observational study was to bring to light the impact of addition of paricalcitrol supplementation on mineral bone, inflammatory and anaemia parameters in patients on Haemodialysis. This study was done to see the effects of vitamin D analogue on anaemia, bone, and inflammation markers in patients on dialysis.

MATERIAL AND METHODS

The Ethics Committee of King Fahd Hospital, Saudi Arabia approved the project and was according to declaration of Helsinki, patients' privacy was ensured.

A total of 210 patients fulfilled the criteria for the study. The study was carried out from Jan to Apr 2017. The patients were recruited from the dialysis unit in the King Fahd Hospital, Medina, Saudi Arabia

Inclusion Criteria: End stage renal disease pts on maintenance haemodialysis and vitamin D deficiency with less than 30 ηg/ml.

Exclusion criteria: The following groups of patients were excluded from the study:

- Patient with vitamin D level in the normal range
- Patients who received vitamin D in the recent past
- Patients with phosphate levels more than 2 and calcium levels more than 2.55 mmol/L
- Patients on calcimimmetics
- Parathyroidectomy patients
- Patients with active infection or malignancy

All dialysis patients except with vitamin D level >30 were prescribed Paricalcitrol given at a dose of 0.04 µg/Kg 3 times a week and titrated to PTH levels. Monitoring was done for 3 months.

Blood samples were taken at baseline and at 6-month follow-up. We checked the parameters after paricalcitrol supplementation. The markers of inflammation used were albumin, ferritin and CRP. Erythropioetic stimulating agent dose was calculated with Hb, ferritin and transferring saturation were analysed to assess the effect of vitamin D analogue replacement on anaemia management. The effect of paricalcitrol was observed with measuring the corrected Calcium phosphate, alkaline phosphatase and total PTH. Serum samples were assayed for the following:

1. 25[OH] vitamin D3 was measured using the 25-[OH] vitamin D3 EIA Kit involving a sunrise plate reader[11]
2. C-reactive protein: Was determined by particle enhanced immunoturbidimetry in which Human CRP agglutinates with latex particles coated with monoclonal anti- CRP antibodies[12]
3. Hb, Calcium Phosphate, and alkaline phosphatase were analysed calorimetrically.
4. Intact PTH, ferritin were analysed with Elisa[13]
5. Transferin saturation was measured as a percentage[14]

Data was formulated using Microsoft Excel 2010 and SPSS. Quantitative variables were determined as means and standard deviation. Qualitative variables were presented as percentages. Paired *t*-test was used to see the link between quantitative variables with symmetrical distribution while Wilcoxin rank test was used to analyse the link of quantitative variables with asymmetrical distribution.

RESULTS

The study population comprised patients on regular haemodialysis. One hundred and twenty patients were excluded (80 with vitamin D>30 ηg/ml, 12 aged less than 20 years, 20 with multiple co-morbidities and admitted and 8 with recurrent GI bleed). Demographic characteristics of the patients are summarized in Table-1. The study was done on 310 patients with age 50±18 years. Male consisted of 55.0%, the patients with diabetes constituted 44%. About 32% of patient's vascular access was a tunnelled line. Mean vitamin D level was 12±15.4 ηg/ml.

Bone markers before and after paricalcitrol supplementation are shown in Table-2. Paricalcitrol supplementation showed significant decrease in PTH levels with paricalcitrol supplementation. There was no significant change in serum calcium, phosphate and alkaline phosphatase levels.

Hb after paricalcitrol supplementation did not show significant statistical difference. Transferrin saturation however improved significantly. Erythropioesis stimulating agent requirement was lower but did not reach statistical significance (Table-3).

The CRP did decrease significantly after paricalcitrol supplementation while albumin did not change significantly (Table-4).

Table-1: Demography

Variables	Result
Number	210
Age	50
Males (%)	55
Diabetes (%)	44.8
Duration on dialysis	4.7±2.1
Patients with tunnelled line	32%
Mean dry weight	60±198
Vitamin D (ηg/ml)	12.6±5.4

Table-2: Effects of vitamin D analogues on mineral bone disorders

	Before	After	Difference (95% CI)	*p*
PTH (ρg/ml)	807.9	641.5	-166.4 (-290.5, -42,5)	0.009
Calcium (corr) (mmol/l)	2.25	2.23	-0.02 (-0.03, 0.07)	0.34
Phosphate (mmol/1)	1.72	1.73	0.1 (-0.48, 0.36)	0.64
Alkaline phosphotase	168.6	173	4 (-44, 35)	0.83

Table-3: Effect of vitamin D Analogue on anaemia parameters

	Before	After	Difference (95% CI)	*p*
Haemoglobin	10.8	10.9	0.1 (-0.48, 0.36)	0.64
Ferritin (ηg/ml)	609.6	541.5	-68.8 (-68, 204)	0.32
Transferrin saturation	23.1	27.4	4.4 (1.6, 7.2)	0.003
ESA dose per week	7737	7262	475 (-976, 1925)	0.83

Table-4: Effect of vitamin D analogue replacement on inflammatory markers

	Before	After	Difference (95% CI)	*p*
C-reactive protein	10±4.22	7±4.16		0.01
Albumin (g/L)	35.2	35.1	0.1 (1.0, 1.1)	0.95

DISCUSSION

The present study shows that supplementation with calcitriol improved the parathyroid hormone level. The factor that calcium and alkaline phosphatase level did not alter was encouraging. However, change in levels of phosphate was not statistically significant after paricalcitrol replacement. Our findings are in harmony with systematic review by Kandula, *et al*, who revealed improvement in PTH level without any alteration in levels of calcium in serum.[15] Patients in our study did not develop significantly higher phosphate levels after addition of paricalcitrol. This nonconformity may be due to dissimilar regimens of vitamin D replacement used in different studies chosen by Kandula, *et al*. This is corroborated by Daroux, *et al*, whose study revealed the increased efficiency of vitamin D3 over vitamin D2 in correcting deficiency of vitamin D in haemodialysis patients.[16] Izquierdo *et al* showed results similar to our study that Paricalcitrol reduces oxidative stress and inflammation in haemodialysis patients[17] supported by other studies.[18] Similarly in kidney transplant recipients paricalcitrol showed good response in secondary hyperparathyroidism and specially the calcium sparing and phosphate sparing effect of vitamin D analogues. Another observation in this study was that patients who are shifted from calcitrol to paricalcitrol required higher doses than who were naïve.[19]

In CKD, hyperparathyroidism develops early as a consequence of 1,25-dihydroxycholecalciferol deficiency[20], diminished expression of the vitamin D receptor[21], Hyperphosphatemia[22], hypocalcemia[23], and PTH resistance[24]. In addition, the inhibition of 1-a-hydroxylation by fibroblast growth factor has been associated with its phosphaturic properties leading to decreased levels of activated vitamin D and in turn further stimulating PTH production.[25] Moreover, the parathyroid glands may by directly stimulated by fibroblast growth factor 23 may, hence further adding to secondary HPT.[26] The substantial decrease in PTH is thus explained by vitamin D supplementation as it primarily inhibits the production and release of PTH from the glands. Further the expression of *m*RNA coding for PTH is inhibited by 1,25[OH]2D.[27]

The current study revealed that addition of Paricalcitrol leads to a notable decrease in CRP levels. This would potentially amount to lower inflammatory burden with a beneficial impact on anaemia management. This finding was similar to one reported by Matias, *et al*, who suggested that cholecalciferol replacement led to improved inflammatory markers in patient on haemodialysis.[28] Improvement in inflammatory markers can be explained by the fact that Vitamin D limits the creation of pro-inflammatory cytokines which in turn calms the tissue specific immune response leading to restriction of inflammation.[29]

Vitamin D exerts its effect by binding to high-affinity VDR (vitamin D receptor) which acts as a ligand-activated transcription factor. Development of some autoimmune disease has been attributed to deficiency of both vitamin D and VDR.[30] It is believed that vitamin D exerts its effect in reducing inflammation is by modifying the expression of several cytokine genes controlled by the VDR.[31,32] Paricalcitrol has been shown to reduce proteinuria in pts with chronic kidney disease.[33] The decreased production of PTH due to addition of vitamin D causes decreased production of inflammatory factors which may explain the influence of vitamin D on CRP.[34] Facts from the study showed that transferrin saturation was improved. This is substantiated by the conclusion of Blanco-Rojo *et al*, that 25-hydroxyvitamin D had a positive impact on transferring saturation.[35] Effect of vitamin D on transferrin saturation is believed to be exerted by its direct stimulation of erythroid precursors.[36] However paricalcitrol addition did not have any influence on haemoglobin or ferritin though lower requirement for erythropoietin use was noticeable. Findings of Matias *et al*, and Goicoechea *et al*, also showed that though no change of haemoglobin was seen after cholecalciferol supplementation but the dosage of erythroid-stimulating agent was decreased.[27,37] This may be due to brief follow-up. The need for lower erythropoietin use in haemodialysis patients on vitamin D has also been demonstrated by Kumar *et al*.[38]

STRENGTHS

This is a prospective study of paricalcitrol supplementation in haemodialysis population in Middle East. We demonstrated to decrease PTH in our people with paricalcitrol and thereby improved bone markers and markers of inflammation and anaemia.

CONCLUSION

Paricalcitrol replacement leads to improvement in secondary hyperparathyroidism in patients on haemodialysis. It showed improvement in inflammatory markers and anaemia parameters.

RECOMMENDATION

We propose paricalcitrol supplementation for patients with stage 5D CKD, especially with hypercalcemia and PTH levels >300 although the hard outcomes like mortality and morbidity need to be studied further.

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