

Comparison of Paricalcitol (I.V) and Alfacalcidol (I.V) in Treatment of Secondary Hyperparathyroidism (SHPT) in Hemodialysis Patients

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¹ Conception of study

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Abstract

Objective: To compare the efficacy of Alfacalcidol (I.V) and Paricalcitol (I.V) for the treatment of secondary hyperparathyroidism (SHPT) in hemodialysis patients.

Material and Methods: An open-label randomized clinical trial was carried out to compare the efficacy of intravenous paricalcitol and alfacalcidol. We recruited 80 patients with end-stage renal disease receiving maintenance hemodialysis in a tertiary care hospital dialysis unit. The participants were randomly divided into two groups. A wash-out period of one week was decided for each patient in whom he/she did not receive any medication for the treatment of hypocalcemia, hyperphosphatemia, or secondary hyperparathyroidism. Afterward, patients received an expanding dosage of alfacalcidol or paricalcitol for a time of about four months, and then after a further washout period of one week, each group received opposite treatment (paricalcitol or alfacalcidol) for a further four months (16 weeks).

Results: The analyzed data for the same end-points revealed no difference between the two groups. No significant statistical difference in terms of calcium levels in both groups was noted. The study also found no big difference in the ability of both drugs to treat secondary hyperparathyroidism, while keeping serum phosphate and calcium levels inside the desired range. The study also found no distinction in the frequency of hypercalcemia and hyperphosphatemia as a side effect of Vitamin D analogue's treatment.

Conclusion: The study concludes that alfacalcidol and paricalcitol are equally effective in the treatment of secondary hyperparathyroidism in the dialysis population. Since Paricalcitol is expensive as compared to alfacalcidol, in an economically challenged country like Pakistan, Alfacalcidol can be a better choice when treating SHPT as we did not find any gross difference in the ability of two drugs to restrict SHPT.

Keywords: Alfacalcidol, Paricalcitol, Secondary hyperparathyroidism, Hemodialysis.

Introduction

Secondary hyperparathyroidism is a common complication of chronic kidney disease especially in patients on hemodialysis. The reduced ability of kidneys to convert vitamin D to its active form results in hypocalcemia. Hyperphosphatemia results due to the decreased ability of kidneys to remove enough PO₄ from the body. Hypocalcemia is the main stimulant for the parathyroid hormone and ultimately patients with CKD go on to develop secondary hyperparathyroidism.

Management of bone mineral disease in dialysis patients sometimes becomes difficult as clinicians face the challenge of treating secondary hyperparathyroidism while keeping calcium and phosphate within normal ranges.¹ Vitamin D analogues are the usual treatment of choice for suppressing PTH levels as it can treat underlying hypocalcemia as well. 1, 25 dihydroxycholecalciferol (calcitriol) is the active form of vitamin D and it not only stimulates the phosphate and calcium reabsorption from the gut but also plays a vital role in bone resorption and bone formation. However, at the same time, reabsorption of calcium and phosphate from the bones and gut can pose a risk for hypercalcemia and hyperphosphatemia. Vascular calcification and coronary artery disease is the leading cause of death in the dialysis population. The basic reason behind these complications is considered to be because of hypercalcemia and hyperphosphatemia.² So in this prospect, a vitamin D analogue that can treat secondary hyperparathyroidism with a limited effect on calcium and phosphorus levels can be of attention.

Alfacalcidol is a commonly used vitamin D analogue in Pakistan; however, paricalcitol is not widely available. The comparison of their efficacy in tackling secondary hyperparathyroidism keeping calcium and phosphorus levels within the normal range can be helpful in our clinical settings.

A study of a randomized controlled trial carried out by Sprague SM et al compared the efficacy of paricalcitol and calcitriol in treating SHPT. The study showed that paricalcitol took less time to bring PTH levels within the desired range as compared to calcitriol with fewer events of hyperphosphatemia.³ Effect on serum calcium levels was comparable in both groups. In another study conducted by Brown AJ et al showed that paricalcitol is less potent in stimulating intestinal calcium and phosphate absorption when compared with calcitriol.⁴

It has been proposed in a few other studies that alfacalcidol has relatively high calcemic and phosphatemic action than paricalcitol. Paricalcitol is much more expensive than alfacalcidol although compliance is not an issue as both are given intravenously at the end of the dialysis session. The study aimed to look at whether paricalcitol worth it as for as suppression of PTH is concerned when compared with alfacalcidol.

Materials and Methods

All the patients included in the study were 18 years old or more. Patients were recruited from a tertiary care hospital and were receiving hemodialysis for at least 6 months. Only stable patients, who were having no history of malignancy or current pregnancy and having a good life expectancy, were included. The wash-out period for drugs (if the patient is receiving any phosphate binder or calcium supplement) was set to be 1 week. Included patients were not receiving any kind of vitamin D analogue, their calcium and phosphate levels were adequately controlled. i.e.; serum corrected calcium less than 10.2 mg/dL and phosphate levels less than 5.5 mg/dL. All the patients had iPTH levels of more than 600 pg/mL.

We divided the patients into two groups. Each group comprised of 40 patients, including males and females. For sample size calculation proportion of patients expected to achieve $\geq 30\%$ decrease in iPTH at the end of the treatment, the period was almost 50% in the alfacalcidol group and 68% in the paricalcitol group. We followed 0.7 controls to recognize a substantial peculiarity (P equal to 0.05 on McNemar's test), 80 individuals had been taken and a randomization list was created by a computer.

The first group of patients with SHPT was treated with alfacalcidol (I.V) for about four months. Afterward, alfacalcidol was stopped and for the next one week patients were off treatment and did not receive any vitamin D analogue, calcium supplement, or phosphate binders. After completing one week wash-out period the same group was treated with intravenous paricalcitol. The second group of patients received paricalcitol (I.V) initially for about four months, subsequently had a wash-out period of one week, and then treated with alfacalcidol for the next four months. Both alfacalcidol and paricalcitol were given immediately after completing the HD session in I.V form. The initial dose of alfacalcidol was 2 μ g, 3 times per week and for paricalcitol, it was 5 μ g, 3 times

per week. However, the dose was adjusted according to the monthly iPTH levels, to keep calcium and phosphorus within an acceptable range.

The calcium concentration of dialysate was set to be 1.5mmol/L and the dialysis concentrate used for each patient was HDA49. During pre-dialysis assessment, weight, blood pressure, pulse, and other vitals were checked for each patient as per routine.

Blood sample collection protocols were designed. Before the start of hemodialysis, all the samples were drawn from the arterial bloodlines. Serum calcium, phosphate, and iPTH levels were checked every month. Based on monthly lab results, required changes in the doses of calcium supplement and phosphate binders were made. The dose of vitamin D analogues was also adjusted based on lab results and clinical judgement.

Results

We decided on the primary efficacy endpoint, secondary outcome, and safety endpoints. The total number of patients achieving equal or greater than 30% reduction in iPTH levels in the last month of treatment with either paricalcitol or alfacalcidol was labelled as the primary efficacy endpoint. The secondary outcome was a change in serum calcium and phosphorus levels, and calcium-phosphorus product falling out of the desired range. Safety endpoints were severe anemia (Hb less than 8), thrombocytopenia (Platelets less than 50), lymphopenia, severe infection, opportunistic infection, persistent hypercalcemia, and hyperphosphatemia or liver abnormalities (ALT and AST more than 3 times upper limit of normal).

Diabetes was found in 37% of the patients. 64 % of the total patients were male. The mean age of the studied patients was 64.5 years (SD 14.5) and the median time on dialysis was 37 months (range 32-62 months) at randomization. The studied patients were in better condition as they had a stable hemoglobin 10.81mg/dL (SD 0.76) and albumin 40.2 g/L (SD 3.7) as compared to other patients.

The analysis of the cross-over data for the percentage changes in PTH revealed a significant period effect (t = -3.946; P). Both vitamin D analogs suppressed secondary hyperparathyroidism successfully during both treatment periods. We could not detect any statistically significant difference in % changes between groups, and there was not any statistically significant difference in the proportion of patients reaching a 30% reduction in PTH. The tables below

show the confirmation of both periods i.e. periods 1 and 2.

Table 1: Changes in PTH during each period of alfacalcidol and paricalcitol treatment

Table 1-A: Period 1

	Period 1		Mean difference % ± SD change and p-value
	Alfacalcidol (n=40)	Paricalcitol (n=40)	
% iPTH changes ±SD	-54.1 ± 5.3	-62.7 ± 3.7	10.7 ± (p=0.102)

Table 1-B: Period 2

	Period 2		Mean difference % ± SD change and p-value
	Alfacalcidol (n=40)	Paricalcitol (n=40)	
% iPTH changes ±SD	-34.8 ± 6.98	-38 ± 6.71	6.02 ± 8.8 (p=0.613)

Table 2: Number of patients reaching treatment goal during each period of alfacalcidol and paricalcitol treatment

	Period 1		p-value
	Alfacalcidol (n=40)	Paricalcitol (n=40)	
≥ iPTH	33 (82%)	37 (93%)	0.190
PTH < 420pg/ml (30% reduction) & Phosphate <5.5mg/dL & ionized calcium <10.2mg/d L	7 (18%)	12 (31%)	0.310
	Period 2		p-value
	Alfacalcidol (n=40)	Paricalcitol (n=40)	
≥ iPTH	24 (59%)	27 (68%)	0.469

PTH < 420pg/ml & Phosphate <5.5mg/dL & ionized calcium <10.2mg/dL	12 (29%)	16 (41%)	0.466
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The analysis of data for the same composite endpoints revealed no difference between groups as shown in Table 3 below.

Table 3: Number of patients with prolonged hypercalcemia or elevated Ca x P product during alfacalcidol or paricalcitol treatment in the period

End Point	No. and Percentages of Patients		p-value
	Alfacalcidol (n=40)	Paricalcitol (n=40)	
Ionized calcium > 10.2 mg/dL and Ca x P > 55 mg ² /dL ² for at least two consecutive blood drawn.	24 (61%)	25 (62%)	1.000
Ionized calcium >10.2mg/dL for at least two consecutive blood drawn and Ca x P ≥ 55 mg ² /dL ² for at least four consecutive blood drawn.	15 (37%)	15 (38%)	1.000

The mean PTH during the last four weeks of treatment was analyzed with baseline PTH as a covariate and a significant baseline PTH x treatment interaction was found (P=0.012) which means that treatment response depended on baseline PTH in the paricalcitol group, whereas alfacalcidol suppressed PTH across all

baseline PTH values. This interaction was also found for numerical changes in PTH (P=0.012), percentage changes of PTH (P=0.036) as for the number of patients reaching a 30% decrease in PTH (P=0.047). Mean PTH during the last four weeks of period 2 were analyzed to describe the reproducibility of this interaction. The same tendency was found, although not statistically significant (P=0.10). However, as there were only 80 patients in this analysis, a small number of patients studied may be the reason for the lack of significance.

In the present study, the differentiated PTH response to paricalcitol across baseline PTH levels may be largely due to the pronounced suppression of PTH at the low baseline levels. 48% of the paricalcitol treated and 29% of the alfacalcidol treated patients reached a PTH level of less than 220 pg/ml (P=0.110). The observed difference in the effect of alfacalcidol and paricalcitol on PTH could be due to a difference in calcium levels. This study did not find any statistically significant difference between the calcium levels in the alfacalcidol group compared to the paricalcitol group when groups were separated according to baseline PTH.

Discussion

Vitamin D is essential for the optimization of bone mineral health. Kidneys produce calcitriol, which is the most important metabolite in upholding calcium and phosphorus homeostasis. In kidney disease, calcitriol levels eventually decrease, resulting in the development of secondary hyperparathyroidism (SHPT).⁵

This randomized control crossover study was designed to observe the clinical effects of two vitamin D analogs and compare their efficacy in terms of treating secondary hyperparathyroidism in the dialysis population. Paricalcitol is a relatively new drug and still, it is not widely available in the market. We compared paricalcitol with conventionally used alfacalcidol to compare their effectiveness and side effects profile. A similar study was carried out by Ditte Hansen et al in 2009 which showed comparable results for both paricalcitol and alfacalcidol.⁶ However, this comparison has never been performed in Pakistan before.

Due to differences between the individuals, the end of the cross over a design was stochastic variation. Deciding the duration of the treatment was a challenge because considering an extensive study period carries the risk of a large number of patients dropping out

sooner than the study finishes. A study carried out in Denmark showed a mortality rate of 21.7% in the Danish dialysis population.⁷ So we considered a study period of 8 months and included only stable patients with good life expectancy. A short study period would have been more liable to get biased results.

We decided on a week washout period for both alfacalcidol and paricalcitol groups as keeping patients of secondary hyperparathyroidism without any vitamin D analog for a longer period of time can pose a risk for developing the serious bone mineral disease (BMD). A smaller wash-out period may reflect the carry-forward effect of drugs from one period to another. The half-life mentioned in literature for I.V alfacalcidol is 36 hours and 14-30 hours for I.V paricalcitol.

Secondary hyperparathyroidism (SHPT), a common complication in the dialysis population, is conventionally treated with vitamin D analogs. Several studies have been carried out in Europe to compare the efficacy of paricalcitol and alfacalcidol. A similar study was carried out by Xinghua Geng et al in China where the researcher compared paricalcitol with other Vitamin D receptor analogs and found that paricalcitol is better than others in controlling iPTH levels. He also found that paricalcitol has mortality benefits compared to other vitamin D analogs.⁸

A randomized multicenter study was conducted by Daniel W Coyne et al in the USA recently which showed that both calcitriol and paricalcitol achieved an effective reduction in parathyroid hormone levels however paricalcitol suppressed iPTH sooner than calcitriol with less incidence of hypercalcemia.⁹ This study was carried out in CKD stage 3-4 patients and not in the dialysis population.

Paricalcitol is a relatively new drug in Pakistan however in the USA, it was launched in 1998. It is generally considered an effective treatment for SHPT, especially in non-compliant patients. Hyperphosphatemia and hypercalcemia are common side effects that need to be tackled effectively. In March 2019, Yang Liu et al published a meta-analysis of the safety and efficacy of paricalcitol in dialysis patients.¹⁰ After reviewing 13 studies, he proposed that Paricalcitol has mortality benefits over other vitamin D analogs however its effectivity in reducing PTH levels was comparable to others. However, two similar studies carried out in renal disease patients by Yifeng Xie et al and Panpan Cai et al could not provide conclusive evidence about the virtual efficacy of paricalcitol over other analogs.^{11,12}

In our study, all the dialysis parameters were kept constant and almost identical for all the patients except dialyzer size and a dose of Tinzaparin (used as an anticoagulant). The selected dialysis patients were in better condition than the general hemodialysis population, as they had higher hemoglobin 10.81mg/dl (SD 0.76) vs. 10.19 mg/dl (SD 2.27) and albumin 40.2 g/l (SD 3.7) vs. 38.8 g/l (SD 4.8).

Vitamin D analogs are frequently associated with hypercalcemia and hyperphosphatemia but that can be controlled with phosphate binders and adjusting the dose of vitamin D analog. The doses were adjusted by a consultant nephrologist on monthly basis after retrieving lab results. Tackling hypercalcemia is important as it can lead to vascular calcification and increased cardiovascular incidents which can result in significant morbidity and mortality.

In the past 20 years, there have been a few paradigm shifts as far as the management of secondary hyperparathyroidism is concerned. Nephrologists have been using different forms of active vitamin D, paricalcitol, and cinacalcet in the near past preferring one over the other depending upon clinical scenario and local protocols. However, there is a need to avoid excessive use of vitamin D analogs and avoid treatment-related complications as mentioned earlier.

Conclusion

The study concludes that there is no difference in the ability of alfacalcidol (I.V) and paricalcitol (I.V) to suppress secondary hyperparathyroidism while keeping phosphate and ionized calcium inside the desired range. Based on this study although carried out in a small number of patients, we suggest that intravenous alfacalcidol is equally effective in treating SHPT and due to the high price of paricalcitol, the former can be a better choice especially in economically challenged countries.

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