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Comparison between paricalcitol versus cinacalcet therapy in the management of secondary hyperparathyroidism among prevalent hemodialysis patients

Maha A. Behairy[1], Osama Mahmoud[1], Ayman Rabie Ibrahim[2*], Aber H. Baki[1]

[1]Internal Medicine and Nephrology, Ain Shams University Faculty of Medicine, Cairo, Egypt
[2]Hemodialysis Center, Domat Al Jandal General Hospital, Al Jouf, Saudi Arabia

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ABSTRACT

Introduction: Secondary hyperparathyroidism (SHPT) is one of the components of chronic kidney disease–mineral bone disorder (CKD-MBD) with significant contribution to the morbidity and mortality among prevalent hemodialysis (HD) patients.
Objectives: This multi-centric experience study aims to compare the effectiveness of intravenous (IV) paricalcitol versus oral cinacalcet and oral cinacalcet plus oral alfacalcidol as treatment regimens of SHPT among chronic HD patients.
Patients and Methods: This is a retrospective observational cohort study, in which 130 prevalent HD patients with SHPT was recruited from three main HD centres of Aljouf region in Saudi Arabia. Patients were divided into three groups; group I (50) HD patients were treated by IV paricalcitol, group II (50) HD patients who received oral cinacalcet plus oral alfacalcidol, group III (30) HD patients were on oral cinacalcet. Serum intact parathyroid hormone (iPTH), calcium (Ca), phosphorus (Po4) and alkaline phosphatase (ALP) tests were assessed at 0, 3, 6, and 9 months.
Results: A total of 130 (61 (47%) females, (53%) 69 males) HD patients with mean age 56.30 ± 19.1 years, and with mean HD duration of 4.86 ± 4.15 years were enrolled in the study. The mean of iPTH is significantly reduced in all studied groups ($P<0.001$). Mean Δchanges in iPTH concentration in groups I, II, III were -242.11 ± 148.75, -225.54 ± 153.91 and -254.83 ± 275.17 respectively; $P>0.05$) with statistical non-significant differences. Increase of Ca×Po4 with paricalcitol group as mean ΔChange in (Ca×PO4) was in the groups I, II, III (15.39 ± 9.46, 1.97 ± 11.74, -2.89 ± 9.37) respectively ($P<0.001$). Our study showed a significant increase in serum phosphorus from the baseline in patients of group II.
Conclusion: IV paricalcitol based regimen assumed to be equally effective in suppressing SHPT in HD patients when compared to the combination of oral cinacalcet with oral alfacalcidol or treatment with oral cinacalcet alone.

Implication for health policy/practice/research/medical education:
The burden of CKD-MBD as SHPT among prevalent hemodialysis patients is one of the serious complications and may be associated with increase the incidence of bone fracture, cardiovascular morbidity and mortality among those patients. Many commercial drugs and different current treatment options were clinically used to control SHPT such as non-selective calcimimetic agents (e.g. cinacalcet), vitamin D as non-selective (e.g. alfacalcidol, calcitriol) and recently the selective vitamin D analogues (e.g. intravenous paricalcitol). The multi-centric survey is mandatory to assess the clinical impact of administration of intravenous paricalcitol in management of progression of SHPT and for further evaluation of the cost-effectiveness of this drug versus other used drug regimens.
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Introduction

Secondary hyperparathyroidism (SHPT) developed in >20% of patients at a glomerular filtration rate (GFR) of <60 mL/min and >70 percentage of patients at a GFR of <30 mL/min (1). Prevention and treatment of SHPT in chronic kidney disease patients (CKD) on hemodialysis (HD) is mandatory as SHPT is associated with increased risk of coronary and vascular calcifications associated

***Corresponding author**: Ayman Rabie Ibrahim, Email: aymanrabie73@yahoo.com

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with increased morbidity and mortality rate (2-4).

The pathogenesis of SHPT in end-stage renal disease patients related to the reduction of calcitriol as a ligand of vitamin D receptor (VDR) results in inhibition of the PTH gene inhibitory system, Ca-sensing receptor (CaSR), VDR abnormalities and also fibroblast growth factor 23 (FGF23) as a pathogen is involved, many significant genetic findings have been established in the process of SHPT.

KDIGO 2017 guidelines recommend maintaining PTH levels at 2- to 9-fold the upper normal limit; the range of 130–600 pg/mL (2,6) with the usage of calcimimetics as cinacalcet, calcitriol, or vitamin D analogues, or a combination of calcimimetics with calcitriol or vitamin D analogues (2B) in patients with CKD G5D requiring PTH-lowering therapy (2).

Non-selective vitamin D stimulates intestinal phosphate and calcium (Ca) absorption as well as phosphate and Ca mobilization from bone, which may lead to hyperphosphatemia and hypercalcemia episodes with increased risk of vascular calcification and cardiovascular disease among patients with CKD (7). Paricalcitol is a selective vitamin D analogue, which revealed significant suppression of intact parathyroid hormone (iPTH) levels with low calcemic and phosphatemic activity (8,9).

Objectives

We aimed to survey the clinical experience and the effectiveness of IV (intravenous) paricalcitol in comparison to cinacalcet and cinacalcet plus alfacalcidol as drug regimens used in the management of SHPT among HD patients.

Patients and Methods

The study population consisted of 130 prevalent HD patients with SHPT, a descriptive retrospective multi-centric study carried out using hospital records for the year 2019 of the three main HD centers in Al Jouf area, Saudi Arabia. Eligibility criteria; HD patients with age ≥18 years, on regular thrice-weekly 4h sessions of conventional HD adequate HD sessions >6 months before the study with a standard bicarbonate-containing dialysate, using biocompatible HD membrane polysulfone low-flux in the majority of studied patients, dialysate Ca concentration 1.5 mmol, patients were maintained at their target dry body weight and received an adequate dose of dialysis (double pool Kt/V≥1.4). Patients with evidence of malignancy, chronic infections, poor general condition or non-compliant with medications were excluded from the study. Eligible HD patients were included in the study were divided into three groups; group I (50) treated by IV paricalcitol, group II (50) received oral cinacalcet with oral alfacalcidol, group III (30) were on oral cinacalcet alone, as different drug regimens of SHPT according to KDIGO guidelines (2).

Data extraction sheet was designed to collect data from clinical records included full clinical history with detailed drug history about doses of phosphate binders, Ca supplements and vitamin D analogues were received by the HD patients, clinical examination and laboratories; complete blood count (CBC), blood urea, serum creatinine, albumin, lipid profile, urea reduction ratio (URR %) calculation (URR = (U pre - U post)/Upre ×100) and Kt/V (K: dialyzer clearance, t: duration of dialysis, V: volume of bodily water) were measured. Serial serum iPTH, corrected Ca, phosphorus (Po4), alkaline phosphatase (ALP) and serum albumin were tested at 0, 3, 6 and 9 months.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**.** The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were chi-square test for categorical variables, to compare between different groups, F-test (ANOVA) For normally distributed quantitative variables, to compare between more than two groups, and post-hoc test (Tukey) for pairwise comparisons, ANOVA with repeated measures for normally distributed quantitative variables, to compare between more than two periods or stages, and post-hoc test (Bonferroni adjusted) for pairwise comparisons, Kruskal–Wallis test for abnormally distributed quantitative variables, to compare between more than two studied groups, and post-hoc (Dunn's multiple comparisons test) for pairwise comparisons, Friedman test for abnormally distributed quantitative variables, to compare between more than two periods or stages and post-hoc test (Dunn's) for pairwise comparisons. Correlation analysis using Spearman's method to assess the association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength and direction of the linear relationship between two variables, rs: Spearman's coefficient. Delta change was calculated as ΔChange = 4^{th} reading - baseline. Percent % of change= (4^{th} reading-baseline)/baseline ×100.

Results

One hundred and thirty HD patients with SHPT were randomly treated with different drug regimens. Group I included 50 HD patients treated with IV paricalcitol at a dose of 5 µg/HD session thrice weekly in 31 (62.0%) of patients and 10 µg/HD session thrice weekly in 19 (38.0%) of the patients. Group II included 50 HD patients treated with oral cinacalcet and oral alfacalcidol, the average alfacalcidol oral dose was 0.25 µg every other day in 11(22.0%) patients, 0.5 µg tablet every other day 27 (54.0%) patients and 1 µg every other day in 12 (24.0%) of patients in this group. Cinacalcet dose was 30 mg tablet

orally in 40 (80.0%) and 60 mg tablet orally in 10 (20.0%) patients of group II. Group III included patients assigned for oral cinacalcet alone with an oral dose of 30 mg once daily in 18 (60.0%) patients and 60 mg tablet orally in 12 of patients (40.0%). No statistically significant differences between studied groups as regard means of age, gender, time of HD, body mass index (BMI) or mean arterial pressure as shown in Table 1 ($P>0.05$). The majority of the studied patients in all groups were on Ca carbonate (Ca based phosphate binders) supplements with an average dose of about 2-2.4 g/d. Accordingly, 10 patients in group I, 13 of patients in group II and 6 patients in group III were also on sevelamer as a non-Ca based phosphate binders with average dose of 3-4 g/d without significant statistical difference between the studied groups regarding using phosphate binders. Serum baseline calcium, phosphorus, alkaline phosphatase and URR showed significant statistical difference in the study as markers of efficacy of treatment of SHPT in all three groups (Table 2).

There was a statistically significant suppression of iPTH levels over the studied period in each group ($P<0.001$) but without significant differences between the studied groups (Table 3, Figure 1). Mean Δ changes in iPTH concentration in-groups I, II, III showed non-statistically significant differences as shown in (Table 4).

Table 5 shows no significant change of mean of serum Ca levels over the studied period in all studied groups ($P>0.05$). Post-hoc test shows a significant difference between group I and group III and between group II and group III, with significantly lower Ca in patients assigned to cinacalcet alone at 9 months. The mean Δ change of serum Ca showed non-significant difference among different groups ($P<0.05$; Table 6). No episodes of hypercalcemia were recorded in group I (IV paricalcitol) or group II (cinacalcet and alfacalcidol). No significant hypocalcemia was noticed in group III (cinacalcet).

Regarding serum phosphorus (PO4) level changes, there was a statistically significant increase over the studied period in group II (cinacalcet and alfacalcidol) only (F=4.11, $P=0.01$). Post-hoc test shows a significant difference between group I and group II and between group I and group III with a lower level in patients assigned to paricalcitol by the end of the study (Table 7). The mean Δ change in serum phosphorus in groups I, II, III was (-0.21 ± 1.29, 0.34 ± 1.11, -0.33 ± 0.9; $P=0.01$) with a significant increase in serum phosphorus in group II versus other studied groups (Table 4). As regards serum ALP levels, no significant differences between groups or within each group over the study period detected (Table 4 and 6). There was a statistically significant correlation between baseline serum iPTH with serum PO4 ($r_s=0.288$, $P=0.001$) ALP ($r_s=0.380$, $P<0.001$) by Spearman's correlations.

Discussion

The development of effective vitamin D analogues in the suppression of PTH without an undesirable low-bone turnover, hypercalcemia and hyperphosphatemia received great attention in the last decades. This is a cohort multi-centric experience study aimed to evaluate retrospectively

Table 1. Comparison between three groups regarding demographic data

		Group I (Paricalcitol)		Group II (Cinacalcet with Alfacalcidol)		Group III (Cinacalcet)		F*	*P* value
		Mean	SD	Mean	SD	Mean	SD		
Age (y)		56.30	19.18	56.00	13.04	56.37	14.21	0.001	0.99
		N	%	N	%	N	%	X²**	
Gender	Male	28	56.0%	25	50.0%	16	53.3%	0.36	0.83
	Female	22	44.0%	25	50.0%	14	46.7%		
Duration of HD (y)		4.86	4.15	4.86	2.86	4.30	2.18	0.33	0.72
Systolic BP (mm Hg)		153.32	20.57	150.52	21.87	157.07	27.50	0.78	0.46
Diastolic BP (mm Hg)		76.72	17.73	77.78	18.43	84.90	17.63	2.13	0.12
Mean Arterial BP (mm Hg)		104.00	17.50	104.80	17.15	110.97	15.98	1.74	0.18
Dry weight (kg)		66.59[a]	16.87	73.32[b]	10.06	75.12[b]	10.72	4.99	0.01
BMI (kg/m2)		26.98	7.35	27.41	4.27	27.18	3.81	0.08	0.93
		N	%	N	%	N	%	X²**	
HTN	No	0	0.0%	9	18.0%	11	36.7%	19.79	<0.001
	Yes	50	100.0%	41	82.0%	19	63.3%		
DM	No	20	40.0%	26	52.0%	12	40.0%	1.79	0.41
	Yes	30	60.0%	24	48.0%	18	60.0%		
CVD	No	17	34.0%	34	68.0%	20	66.7%	13.94	0.001
	Yes	33	66.0%	16	32.0%	10	33.3%		

*One-way ANOVA test (a,b: post hoc test); **Chi-square test.

Table 2. Comparison of three groups regarding baseline (1st reading) laboratories

Laboratories	Group I		Group II		Group III		F*	*P* value*
	Mean	SD	Mean	SD	Mean	SD		
Serum Ca (mg/dL)	8.59[a]	0.74	8.57[a]	0.74	8.21[b]	0.53	3.22	0.04
Po4 (mg/dL)	5.24[a]	1.52	5.73	1.44	6.19[b]	1.12	4.46	0.01
PTH (pg/mL)	550.22	149.19	597.58	171.72	609.53	133.62	1.78	0.17
ALP (IU/L)	103.52[a]	59.44	116.30	52.35	142.33[b]	78.33	3.71	0.03
Serum albumin (g/dL)	3.51	0.37	3.47	0.34	3.50	0.32	0.18	0.83
Serum creatinine (mg/dL)	9.65	2.75	10.02	2.62	10.47	2.42	0.93	0.40
URR%	70[a]	10	67	8	66[b]	7	3.06	0.05
Kt/V	1.37	.26	1.28	.22	1.26	.17	2.97	0.06
Hgb (g/dL)	9.96	1.31	10.05	1.26	9.96	1.08	0.09	0.92
Cholesterol (mg/dL)	147.24	39.93	158.32	39.37	155.17	36.06	1.06	0.35
Triglycerides (mg/dL)	167.61	105.29	174.56	108.97	168.20	94.56	0.06	0.94

*One-way ANOVA test (a,b: post hoc test) .P-value significant <0.05.
Ca: calcium, PO4: phosphorus, PTH: parathyroid hormone, ALP: Alkaline phosphatase, URR%: Urea reduction ratio, Kt/V: (K: dialyzer clearance, t: duration of dialysis, V: volume of bodily water), High : hemoglobin.

Table 3. Comparison between three groups regarding change in PTH level during follow up

iPTH level readings	Group I (Paricalcitol)		Group II (Cinacalcet with Alfacalcidol)		Group III (Cinacalcet)		Within subject effect		Between subject effect
	Mean	SD	Mean	SD	Mean	SD	Time	Time * group	Group
0 months	550.22	149.19	597.58	171.72	609.53	133.62	<0.001*	0.57	0.15
3 months	414.86	185.75	507.52	364.31	531.70	332.90			
6 months	333.30	149.99	380.62	243.59	339.83	184.91			
9 months	308.11	129.88	372.04	208.98	354.70	319.13			

General linear model repeated measure ANOVA analysis was used.
*Post hoc test shows a significant difference between all-time points except between 6 months and 9 months.

the clinical values of IV paricalcitol administration, a selective vitamin D analogue versus other routine drug regimens as a combination of oral alfacalcidol plus oral cinacalcet or oral cinacalcet only to reach target PTH level according to KDIGO guidelines recommendations.

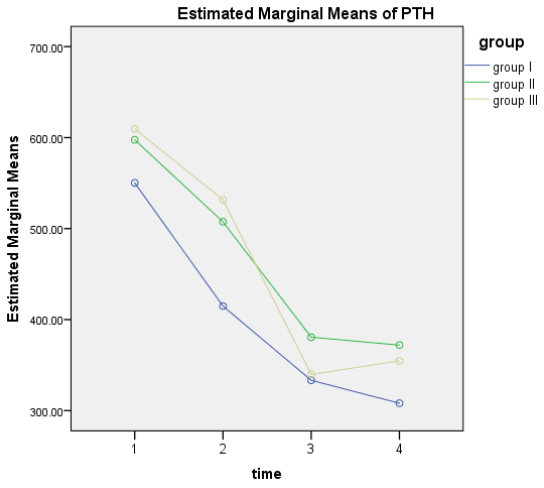

Figure 1. Comparison of HD patients groups regarding mean PTH levels during the studied period.

Parathyroid hormone concentration was significantly suppressed during the follow up over 9 months in all studied groups. IV paricalcitol reduced iPTH level by mean of -242.11 pg/mL (42.53%) compared with combination alfacalcidol and cinacalcet -225.54 pg/mL (38.79 %) and in cinacalcet group -254.83 pg/mL (44.52%), as no statistically significant differences, which indicates that IV paricalcitol equally effective in iPTH suppression and not superior to other drug regimens among HD patients with SHPT in this study.

In contrast to the previous multicentric randomized controlled trial by Ketteler et al in 2012 who showed, at the end of 28-week follow-up of HD patients, the mean iPTH reduction was -244.2 ρg/mL in the IV paricalcitol group as compared with -78.4 ρg/mL in a group of patients using cinacalcet plus low-dose vitamin D with a greater reduction in iPTH with using oral or iv paricalcitol (10). The pooled results of the meta-analysis done by Liu et al in 2019 reported that the serum PTH level was significantly reduced in both the paricalcitol group and other vitamin D receptor activator (VDRA) group, however, paricalcitol was associated with a greater serum iPTH change than other VDRAs (11).

We reported in this study that there was no statistical significance in mean change of Ca level at end of 9 months

Table 4. Comparison between the different studied groups according to different parameters

Change of studied parameters over 9 months	Group I (n = 50)	Group II (n = 50)	Group III (n = 30)	Diff. in change bet G I & G II	Diff. in change bet G I and G III	Diff in Change bet G II and G III
Serum Ca (mg/dL)						
ΔChange	0.02 (0.74)	-0.08 (0.57)	-0.05 (0.51)	-0.10 (-0.37-0.16)	-0.07 (-0.38-0.23)	0.03 (-0.22-0.29)
% of change	0.88 (9.16)	-0.52 (6.80)	-0.37 (6.55)	1.40 (-1.80-4.60)	1.25 (-2.56-5.06)	-0.15 (-3.23-2.94)
PO_4 (mg/dL)						
ΔChange	-0.21 (1.29)	0.34 (1.11)	-0.33 (0.98)	0.55* (0.08-1.03)	-0.12 (-0.67-0.42)	-0.68* (-1.17--0.19)
% of change	-0.05 (22.62)	9.30 (21.40)	-4.44 (15.88)	-9.25* (-17.99-0.51)	4.49 (-4.11-13.09)	13.74* (4.76-22.72)
iPTH (pg/mL)						
ΔChange	-242.11 (148.75)	-225.54 (153.91)	-254.83 (275.17)	16.57 (-43.50-76.64)	-12.72 (-107.0-81.56)	-29.29 (-124.7-66.1)
% of change	42.53 (23.64)	38.79 (24.55)	44.52 (39.32)	3.74 (-5.83-13.31)	-1.99 (-17.97-14.0)	-5.73 (-19.93-8.47)
ALKP (IU/L)						
ΔChange	-7.50 (53.37)	7.70 (48.89)	-2.33 (67.43)	-15.20 (-35.51-5.11)	-5.17 (-32.29-21.95)	10.03 (-15.94-36.01)
% of change	12.64 (41.28)	0.48 (45.89)	1.01 (34.63)	12.16 (-5.16-29.48)	11.63 (-6.27-29.53)	-0.53 (-19.87-18.81)

Ca: calcium, PO4: phosphrous, PTH: parathyroid hormone, ALP: alkaline phosphatase.
Data in Groups I, II, and III are expressed in mean (SD) while differences are shown in mean & 95% CI. * Statistically significant at $P \leq 0.05$.

Table 5. Comparison between three groups regarding the change in Ca level during follow up

Serum Ca level	Group I (Paricalcitol)		Group II (Cinacalcet with Alfacalcidol)		Group III (Cinacalcet)		Within subject effect		Between subject effect
	Mean	SD	Mean	SD	Mean	SD	Time	Time * group	Group
0 months	8.59	0.74	8.57	0.74	8.21	0.53	0.75	0.48	0.001*
3 months	8.56	0.48	8.41	0.66	8.26	0.54			
6 months	8.68	0.57	8.48	0.57	8.20	0.56			
9 months	8.61	0.48	8.49	0.46	8.16	0.51			

General linear model repeated measure ANOVA analysis was used.
*Post hoc test shows a significant difference between group I and group III and between group II and group III.

Table 6. Comparison between three groups regarding the change in ALP level during follow up

ALP level	Group I (Paricalcitol)		Group II (Cinacalcet with Alfacalcidol)		Group III (Cinacalcet)		Within subject effect		Between subject effect
	Mean	SD	Mean	SD	Mean	SD	Time	Time * group	Group
0 months	103.52	59.44	116.30	52.35	142.33	78.33	0.75	0.48	0.001*
3 months	109.62	78.41	106.56	53.92	150.13	106.78			
6 months	107.66	77.77	107.66	62.51	140.30	109.36			
9 months	111.02	84.74	108.60	56.15	144.67	114.07			

General linear model repeated measure ANOVA analysis was used.

of follow up, although there was an increase in Ca level in paricalcitol level and decrease in Ca with cinacalcet drug ($P > 0.05$). The comparison between the studied groups showed insignificant change in the mean Ca by three-drug regimen as mean ΔChange in paricalcitol, the combination of alfacalcidol plus cinacalcet versus cinacalcet only was (0.02 ± 0.74, -0.08 ± 0.57, -0.05 ± 0.51) mg/dl respectively ($P > 0.05$). In comparison to previous studies as in Liu et al, where they found no significant difference in serum Ca level change between the paricalcitol group and other VDRAs group and that cinacalcet plus active vitamin D significantly improved the blood Ca compliance rate in comparison to cinacalcet alone (10). Ketteler et al in a study observed that oral paricalcitol increased the Ca level by 0.3 mg/dL, whereas cinacalcet reduced it by 0.7 mg/dL (10).

KDIGO guidelines 2017 suggested that in adult patients with CKD G3a–G5D, mild and asymptomatic hypocalcaemia is better than developing hypercalcemia and maintaining serum Ca in the low normal range (2D) (2). This was observed with cinacalcet containing regimens to avoid the hazard of vascular calcification and increased cardiovascular morbidity with hypercalcemia episodes in HD patients.

Table 7. Comparison between three groups regarding the change in PO_4 level during follow up

Serum PO_4 level	Group I (Paricalcitol)		Group II (Cinacalcet with Alfacalcidol)		Group III (Cinacalcet)		Within subject effect		Between subject effect
	Mean	SD	Mean	SD	Mean	SD	Time	Time * group	Group
0 months	5.24	1.52	5.73	1.44	6.19	1.12	0.07	0.05	<0.001*
3 months	5.12	1.14	6.21	1.33	6.32	1.42			
6 months	5.25	1.64	6.24	1.34	6.12	1.31			
9 months	5.03	1.20	6.08	1.06	5.86	1.22			

General linear model repeated measure ANOVA analysis was used.
*Post hoc test shows a significant difference between group I and group II and between group I and group III.

In the current study, there was a significant increase in the mean PO4 at 9 months follow up in group II (alfacalcidol and cinacalcet) but no significant change in serum PO4 in group I (IV paricalcitol) or in group III (cinacalcet only). There was a significant difference between the mean change of serum phosphorus in group I (paricalcitol) [-0.21 ± 1.29] and that in group II (alfacalcidol plus cinacalcet) was [0.34 ± 1.11]. A significant difference between group II and group III as mean a change of serum phosphorus was [-0.33 ± 0.98] in group III (cinacalcet only), but no significant difference between group I and group III as regard mean of change of serum phosphorus at 9 months follow up.

Ketteler et al in their study showed that paricalcitol was more effective than cinacalcet in achieving the optimal control of Ca and phosphorus (10). The study by Ong et al showed no significant difference in serum phosphorus changes between the paricalcitol (-0.01 mmol/L) and calcitriol groups (0.27 mmol/L) at the 24 months (12).

The monitoring of serum ALP is important as PTH level can give additional information about bone turnover in HD patients, and increased level of ALP may be associated with greater risks of hospitalization and death among HD patients (13). In the VITAL study, Coyne et al observed that ALP decreased progressively, accompanying the PTH decrease, with a partial relationship between changes in PTH and changes in ALP values. They suggested that the decrease in ALP was a consequence of not only PTH reduction but also a direct suppressive effect of paricalcitol on osteoblasts (14). Additionally, Zawierucha et al found a statistically significant reduction in serum ALP at 3-months follow up on paricalcitol treatment of 36 patients on HD with SHPT including 11 patients who additionally received cinacalcet (15). However, we did not observe any significant differences statistically as regard means of change or percentage of the change in serum ALP between studied groups.

The relatively high-cost of IV paricalcitol drug and the similar effectiveness as the combination of alfacalcidol plus cinacalcet or cinacalcet alone to reach target PTH level and maintain normal Ca without an episode of hypercalcemia may limit the clinical usage of IV paricalcitol, but still, the IV paricalcitol has a statistically significant minor change in phosphorus level without an episode of hyperphosphatemia versus alfacalcidol plus cinacalcet as we observed in the current study.

Conclusion

IV paricalcitol based regimen assumed equally effective in suppressing SHPT in prevalent HD patients when compared to the combination of oral cinacalcet plus oral alfacalcidol or treatment with oral cinacalcet alone, with less incidence of hyperphosphatemia with paricalcitol or cinacalcet in comparison to alfacalcidol containing regimen.

Limitations of the study

Retrospective study and a limited number of centers using IV paricalcitol as a treatment for hyperparathyroidism in HD patients in the area of the study.

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Authors' contribution

MB has made substantial contributions to the conception and design of this study, revised and analyzed the patient data, involved in writing and drafting of the manuscript and has given final approval of the version to be published. OM made substantial contributions to conception and design, revised and analyzed the patient data and has given final approval of the version to be published. AI made substantial contributions to acquisition of data, involved in writing the manuscript and has given final approval of the version to be published. AB made substantial contributions to conception and design, analysis and interpretation of data; he has been involved in drafting the manuscript and revising it for important intellectual content; and he has given final approval of the version to be published. All authors read and approved the final manuscript file.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and approved by Ain-Shams University Hospital Research Committee (Ethics committee reference number 000017585). Data extracted sheets were collected and analyzed after following ethical considerations of the main hospitals in Aljouf region, Saudi Arabia. Oral consent for participation was taken from all patients, local ethics committee ruled that no formal ethics approval was required in this study as it is not a clinical trial. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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