Magna Scientia Advanced Research and Reviews

eISSN: 2582-9394

Cross Ref DOI: 10.30574/msarr

Journal homepage: https://magnascientiapub.com/journals/msarr/

(RESEARCH ARTICLE)

The effect of paricalcitol and cinacalcet on parathyroid hormone in patients undergoing chronic hemodialysis and serum calcium and phosphorus oscillation

Elvedin Osmanovic * and Hidajet Rahimic

Public Health Center Zivinice, Center for hemodialysis, Zivinice, Zip code 75270, Bosnia and Herzegovina.

Magna Scientia Advanced Research and Reviews, 2023, 07(01), 134–144

Publication history: Received on 06 January 2023; revised on 16 February 2023; accepted on 18 February 2023

Article DOI: https://doi.org/10.30574/msarr.2023.7.1.0028

Abstract

Chronic kidney disease (CKD) is one of the leading public health problems in the world, and according to research conducted on different races and in different parts of the world, approximately one in 10 adults has some form of kidney damage. In stage 3 CKD, the kidneys lose the ability to remove excess phosphorus that accumulates in the body, leading to hyperphosphatemia, which promotes an increase in parathyroid hormone (PTH), and the appearance of secondary hyperparathyroidism. It is associated with increased morbidity and mortality and negatively affects the quality of life of patients with chronic kidney disease. It is generally considered that parathyroid hormone is a systemic "toxin" in CKD and its increased secretion is a sign of progression of kidney disease. Homeostasis of calcium and phosphorus is maintained through a complex connection between bones, intestines, kidneys and parathyroid glands. A retrospective - prospective study will be conducted in the hemodialysis center of the Živinice Health Center. 49 patients suffering from secondary hyperparathyroidism will be included in the study. Patients are of both sexes, aged 18 to 85 years. As part of secondary hyperparathyroidism in hemodialysis patients, 75.5% of patients had PTH values below 1000 pg/ml, while 24.5% had PTH values above 1000 pg/ml. A decrease in serum Ca and P values was recorded in 32% of subjects who were treated with paricalcitol. A decrease in serum Ca and P values was recorded in 56% of cases. Observing the effect of paricalcitol and cinacalcet, it is observed that the greatest reduction in PTH values in patients who had PTH values higher than 1000pg/ml - treated with cinacalcet is 44%.

Keywords: Kidney disease; Parathyroid hormone; Calcium; Phosphorus

1. Introduction

Chronic kidney disease (CKD) is one of the leading public health problems in the world and according to studies conducted in different races and in different parts of the world, approximately one in 10 adults has some form of kidney damage.[1] CKD occurs when the kidney is no longer able to fulfill its main functions of excreting metabolic products, maintaining acid-base balance, and hormone secretion. Many diseases lead to chronic kidney failure. Diabetic and hypertensive nephropathy are the leading causes of advanced chronic renal failure[2].

CKD is associated with an increased incidence of cardiovascular disease and premature death. It is defined as a disorder of renal structure or function that persists for at least 3 months and has health consequences. It is classified by cause, glomerular filtration and albuminuria. In the early stages of CKD there is a disturbance in the homeostasis of minerals with severe consequences for the whole organism. In the Stage 3 of CKD, kidneys lose the ability to remove excess phosphorus that accumulates in the body leading to hyperphosphatemia, which generates an increase in parathormones (PTH), a decrease in vitamin D, and an increase in FGF23 (fibrobrast-growth factor). This is where the kidney plays a key role in hormone homeostasis. A decrease of kidney function leads to low conversion of vitamine D in its active state, which reduces the absorption of calcium in the intestine[3]. Another problem is the resistance to vitamin D due to reduced expression of receptors on target cells. The body by increasing FGF23 tries to maintain homeostasis

* Corresponding author: Elvedin Osmanovic

of phosphorus by increasing its excretion. The body tries to stimulate phosphaturia and improve the absorption of calcium by increasing PTH, but again with the problem of efficiency due to the resistance of cells to the action of PTH. A vicious cycle is created that ultimately leads to the development of secondary hyperparathyroidism (SHPT) with extremely high PTH, hyperphosphatemia and hypocalcemia that represent cardinal features of the advanced stage of HBB[4].

1.1. Secondary hyperparathyroidism in patients with CKD

SHPT is one of the most common complications in patients with CKD, and CKD is the most common cause of SHPT. It is characterized by elevated values of PTH in the blood, and disorders of bone metabolism and minerals metabolism, primarily calcium and phosphorus, where we primarily find hyperphosphatemia and hypocalcemia as the main features of advanced CKD[5]. It is associated with increased morbidity and mortality and negatively affects the quality of life of patients with CKD. It is generally considered that PTH is a systemic "toxin" in CKD and its increased secretion is a sign of progression of renal disease. Calcium and phosphorus homeostasis is maintained through a complex relation between bones, intestines, kidneys, and parathyroid glands. SHPT occurs as an adaptive pathophysiological process in response to worsening renal insufficiency. PTH is a hormone that is synthesized and secreted from the main cells of the parathyroid glands and acts directly on target cells in kidneys and bones via specific transmembrane receptors. The main regulators of its excretion are calcium, phosphorus and 1,25 – dihydroxy – vitamin D3 (calcitriol or active vitamin D). The basic mechanism of PTH action in the kidneys is to suppress the reabsorption of phosphate in the proximal tubules and to stimulate the reabsorption of calcium in the ascending limb of the loop of Henle, the distal tubule and the collecting tube[6].

1.2. Disorders of bone mineral metabolism in CKD (CKD-MBD)

CKD-MBD is a significant complication of SHPT, it includes disorders of calcium, phosphorus, PTH and/or vitamin D, with disorders of metabolism and bone remodeling with changes in mineralization, linear growth, strength and volume of bone tissue, as well as extracorporeal calcification, that is, calcification of blood vessels and soft tissues, and CKD-MBD as one of the main indicators of increased morbidity and mortality in patients on hemodialysis. In recent years, clinical studies have shown that by regulating PTH levels and controlling mineral homeostasis (calcium, phosphorus, calcium product and phosphorus), morbidity and mortality can be reduced in patients with SHPT. Current treatment options refer to the modulation of calcium and phosphorus balance by hemodialysis, adequate food intake, phosphorus binders, vitamin D analogues (most often Calcitriol, Paricalcitol, Alfacalcidol, Doxercalciferol) and newer calcimimetics that reduce PTH alone (Cinacalcet) or in combination with Calcitriol. Treatment of SHPT is still a challenge for clinicians. Patients whose drastically high PTH values (>1100 pmol / L) cannot be regulated by medical therapy undergo parathyroidectomy as the ultimate measure of PTH regulation[7].

Regardless of dietary measures and taking phosphate binders, almost all patients on hemodialysis develop SHPT. The active forms of vitamin D3 and its analogues (Paricalcitol) can successfully keep hyperparathyroidism under control. Its downside is that it can cause hypercalcemia. Calcimimetics are drugs that, with their molecules, successfully block calcium receptors on the parathyroid glands, thereby reducing the secretion of PTH. Cinacalcet belongs to this group of drugs. Its great advantage over vitamin D3 and its analogues can be applied in hypercalcemia. The indicator of successful therapy is the reduction of serum PTH, i.e. the maintenance of PTH in optimal values[8].

Excessive doses of vitamin D causes hypercalcemia, increase the risk of vascular calcifications, increase arterial stiffness and left ventricular hypertrophy. Vitamin D substitution increases the level of 25(OH)D and 1.25(OH)2D, lowers the level of PTH, and it does not increase the risk of hyperphosphatemia. It is questionable whether this substitution has a beneficial effect on the cardiovascular system and bone metabolism. Calcimimetics are drugs that allosterically activate CaSR and potentiate the effect of calcium which is an orthosteric agonist of CaSR. For now, only Cinacalcet is available on the market. Unlike vitamin D analogues, Cinacalcet does not increase the absorption of calcium and phosphorus in the intestine. Cinacalcet alone, and even better in combination with a low dose of calcitriol analogues lowers PTH[9].

Objectives

- Determine the effect of Paricalcitol and Cinacalcet on parathyroid hormone (PTH) values.
- Determine the effect of Paricalcitol and Cinacalcet on the values of Ca and P in the blood.
- Therapeutic recommendation in the treatment of secondary hyperparathyroidism (SHPT).

2. Material and methods

A retrospective – prospective study will be conducted at the Center for hemodialysis within Public Health Center Živinice. 49 patients (subjects) will be included in the study. The patients are of both gender between18 to 85 years of age. The research will be retrospective-prospective in nature and will be conducted during period from 1 June 2022 until 1 February 2023. The criteria for participation in the study are patients who are on a chronic hemodialysis program, have elevated PTH values, in the treatment of secondary hypeparathyroidism use paracalcitol or cinacalet, have not had yet parathyroidectomy surgery. Data will be collected from the patient's medical records, PTH and laboratory findings.

Participants will be divided into four groups:

- The group has 13 patients who have PTH values varying from 180 to 300 pg.
- The group has 12 patients who have PTH values varying from 301 to 600pg.
- The group has 12 patients who have PTH values varying from 601 to 1000pg.
- The group has 12 patients that have PTH values of more than 1000 pg.

Paricalcitol is a synthetic, biologically active analogue of Calcitriol with the properties of vitamin D. Patients have received 5 mcg of Paricalcitol ampoules in the first group 1x1 per week iv. in the second group 2x1 week iv. and in the third group 2x1 iv versus value of PTH.

Cinacalcet is a cachimimetic, and is a newer generation of medicine for the treatment of secondary hypeparathyroidism.

Patients in the fourth group were administered Cinacalcet in tablets (as cinacalcethloride) at a dose of 30mg 2x1 tablets per day orally.

The PTH values in the patients were determined 2 times over the course of the study.

All data will be processed using descriptive statistics methods, where the numerical data will be presented with appropriate measures of central tendency and measures of variance, and clearly displayed with appropriate tables and graphs. Nonparametric methods and tests will be used to calculate statistical significance: the C2 test will be used to calculate differences within groups, and the Kruskall-Wallis test will be used to calculate differences between groups with the C2 test and if there is a statistically significant difference between groups, additional testing will be carried out between groups using the Mann-Whitney U test. For parametric data, differences between groups will be calculated using one-way analysis of variance (ANOVA), with subsequent calculation of Tukey'S HD test if there are differences between groups, and will be used Student's "t" test for dependent samples. Statistical hypotheses were tested at $\alpha = 0.05$ level, i.e. the difference between groups in the sample will be considered significant if $p < 0.05$. Statistical processing will be carried out with the support of biomedical application software called "MedCalc for Windows version 12.4.0", Copyright © 1993-2013, and mainly with the use of software "SPSS Statistics 17.0", Copyright © 1993-2007.

3. Results

A total of 53 patients were included in the study, of which 33 were male and 20 female patients. The difference in the frequency of male and female respondents is also statistically significant for the benefit of male respondents (χ^2=10.025; df=1; p=0.001).

Table 1 Distribution by gender

	Total number	**Percentage**
Man	29	59.2
Woman	20	40.8
Total	49	100.0

(χ^2=10.025; df=1; p=0.001)

Observed by the study groups, the Ca and P values show different deviations, and the largest differences are observed by comparing patients with a PTH value less than <180pg and patients with a PTH value >1000pg. The differences are statistically significant (χ^2=7.34; df = 2; p<0.001). This is directly related to elevated PTH values, and the largest change was observed in the group of patients who had PTH values above 1000pg, which is statistically significant (Pearsons r=0.172; p=0.034). All patients were treated for elevated serum levels. Ca and P receive vitamin D sterols or phosphate-binding substances (Table 2).

Table 2 Blood levels of Ca and P before treatment with Paricalcitol and Cinacalcet

group	Ca			P		
	Min.	Max.	Average value	Min.	Max.	Average value
I	2.16	2.53	2.41	0.81	1.45	1.33
II	2.15	2.74	2.49	0.86	1.37	1.35
III	2.21	2.86	2.51	1.13	1.74	1.43
IV	2.25	3.01	2.60	1.24	2.2	1.64

(χ^2=7.34; df = 2; p<0.001); (Pearsons r=0.172; p=0.034)

Table 3 Blood levels of Ca and P after treatment with paricalcitol

group	Ca			P		
	Min.	Max.	Average value	Min.	Max.	Average value
I	2.12	2.47	2.19	0.79	1.41	1.10
II	2.16	2.53	2.34	0.81	1.35	1.20
III	2.19	2.58	2.42	0.98	1.54	1.41

There was a decrease in serum levels of Ca and P and the Ca x P ratio was recorded in 32% of patients. Comparing the decrease in the values of Ca and P expressed in the average values per study groups, statistical significance is observed (χ^2=8.14; df = 1; p<0.0098).

Cinacalcet-treated patients who had high serum Ca and P values showed a significant decrease in serum Ca and P values and a decrease in the product of Ca x P compared to those treated with Paricalcitol. Decreases in serum Ca and P were observed in 56% of cases. The group of treated patients with Cinacalcet has the greatest reduction in Ca and P, and this difference compared to other study groups is due to the use of Cinacalcet (χ^{Two}= 9.52; df = 3; p =<0.001), as presented in (Table 4).

Table 4 Blood levels of Ca and P after treatment with Cinacalcet

group	Ca			P		
	Min.	Max.	Average value	Min.	Max.	Average value
IV	2.18	2.2	2.19	1.24	1.45	1.33

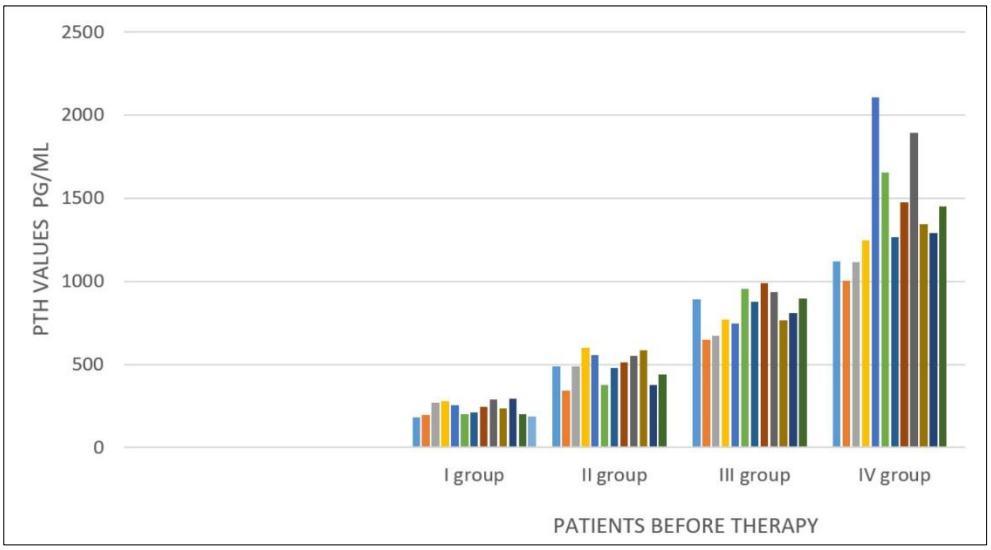

Figure 1 PTH values prior to treatment by study groups

In secondary hemodialysis patients, 75.5% of patients had PTH values below 1000 pg/ml, while 24.5% had PTH values above 1000pg/ml, as presented in Figure 1.

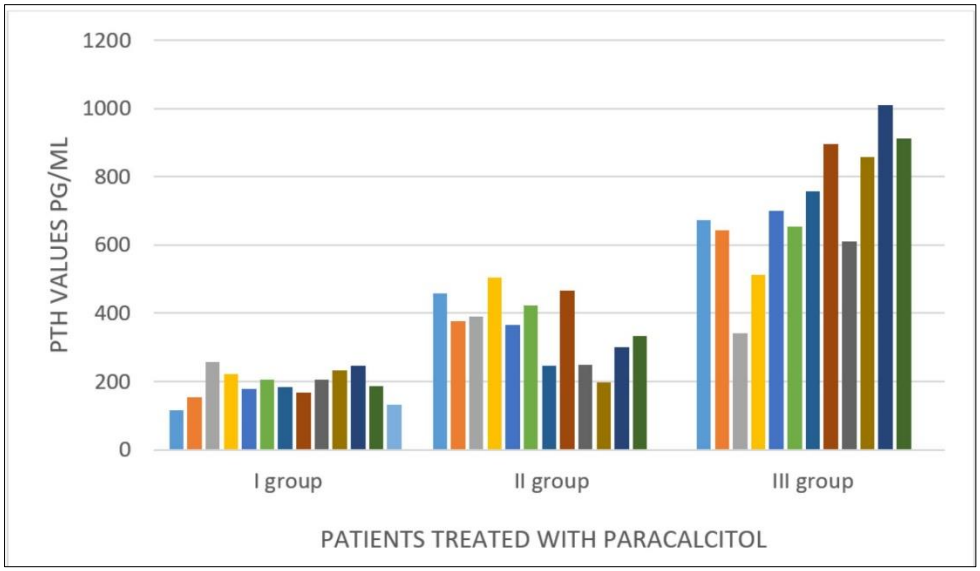

Figure 2 PTH after treatment with Particalcitol

There is a decrease in PTH after treatment with paricalcitol, and there is a statistical significance (χ^2= 8.12; df = 3; p =<0.001). Looking at the study groups, the greatest decrease in PTH was observed in patients who had PTH values of 301-600pg/ml. A significant reduction in the therapeutic effect of paricalcitol was observed in patients with PTH values of 601-1000pg / ml, (χ^2=30.869; df=9; p<0.001), as presented in Figure 2.

Comparing the differences in PTH values before and after therapy, the most significant change was observed in the group of patients with PTH values above 1000PG, which is statistically significant (Pearsons r=0.121; p=0.041). By testing the correlation between the groups, it was determined that there is a one-way correlation between the groups (Pearson's r=0.136; p=0.043), which is shown in Figure 3.

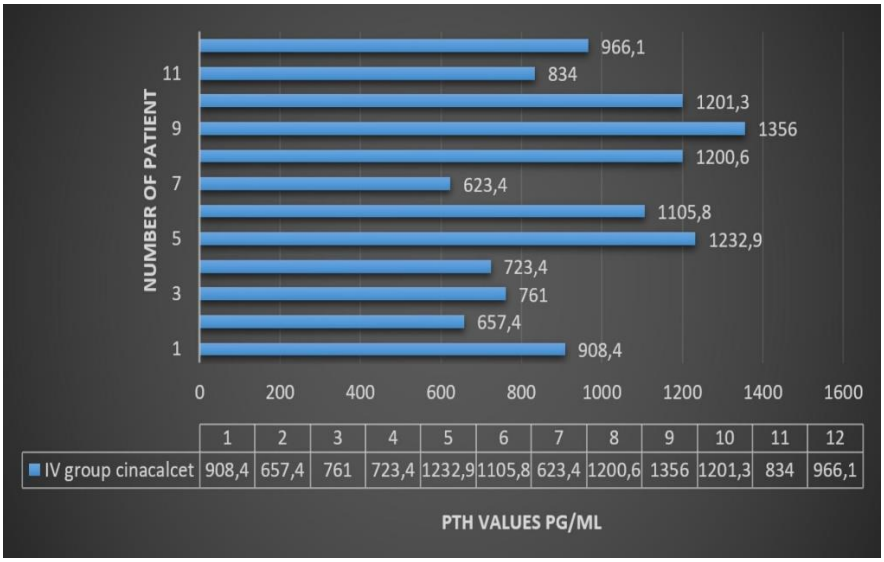

Figure 3 Decrease in PTH values after therapy with Cinacalcet

	PTH pg/mmol (paricalcitol)		PTH pg/mmol (cinacalcet)
man No18	165.7	man No5	211.8
woman No19	172.5	woman No7	223.2
age 18-30	179.5	age 18-30	218.2
age 31-50	168.3	age31-50	224.9
age 50-80	159.5	age 50-80	198.9

Figure 4 The effect of gender and age factors on reducing the level of PTH

In the study of the effect of Paricalcitol and Cinacalcet on the reduction of PTH levels, it was observed that there was no significant difference in the effect of Paricalcitol and Cinacalcet on the reduction of PTH levels (χ^{Two}=5.2; df = 2; p<0.001).

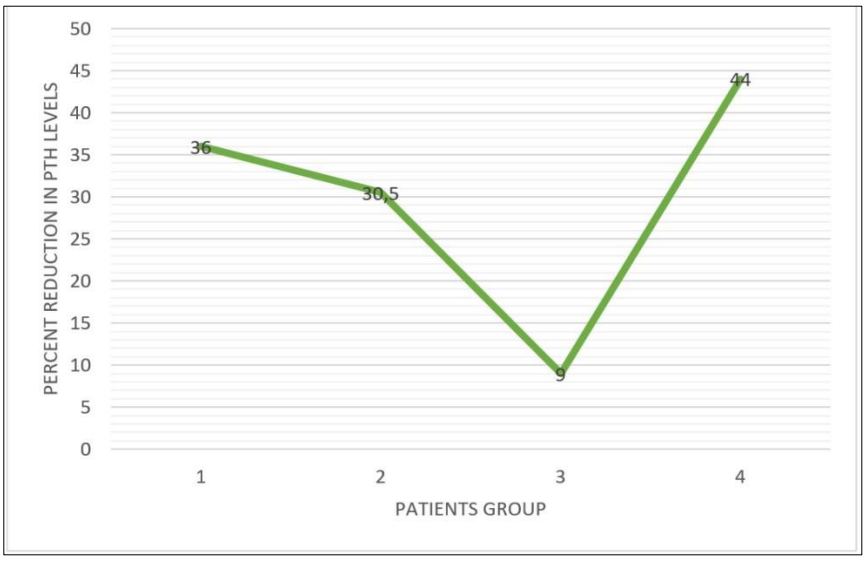

Figure 5 The percentage of PTH levels per group

Looking at the effect of Paricalcitol and Cinacalcet, it was observed that the greatest decrease in PTH values was in the fourth group (patients who had PTH values greater than 1000pg/ml – treated with cinacalcet) at 44%. The reduction in PTH levels of patients of group 3 under the influence of Paricalcitol in patients of group 3 (PTH 601 to 1000 pg/ml) was the least, only by 9%. Statistically, there is a significant difference in the decrease in the value of PTH in patients under Cinacalet (χ^2=11.9; df = 4; p<0.001).

The mean values of PTH in individual study groups, as well as their average values are presented in Table 5. By testing the correlation between groups, it was found that there is a one-way correlation (Pearson's r=0.136; p=0.043). According to the Kruskal-Wallis test, this difference is statistically significant (χ^2=30.869; df=9; p<0.001). In patients with PTH values above 180pg/ml, 9 cases with PTH values above 1000pg were reported, which is statistically significant (χ^2= 0.775; df = 9; p = 0.001), and represents the end values. (Table 5).

Table 5 Presents the PTH values of the study groups prior to the therapy

Mann-Whitney U		**Significance level**	**The average value of PTH before therapy**
Patients with PTH 180-300 pg / ml	Z = -5.186	p<0.001	191.4
Patients with PTH 301-600 pg/ml	Z = -2.316	p=0.009	359.2
Patients with PTH 180-300 pg / ml	Z = -3.530	p<0.001	713.9
Patients with PTH > 1000 pg/ml	Z = -1.830	p<0.074	964.1

Pearsons r=0.121; p=0.041

The group of treated patients with Cinacalcet has the highest mean rank and the highest median, which indicates that this difference is most conditioned by the PTH values in this group (Table 5).

Table 6 Differences between groups in the observed level of PTH before and after therapy

		N	**Mann-Whitney U**	**Significance level**	**The average value of PTH**
PTH level before therapy	Patients with PTH 180-300 pg / ml	12	Z = -5.186	24.635	191.4
	Patients with PTH 301-600 pg/ml	11	193.88	27.885	359.2
	Patients with PTH 180-300 pg / ml	18	172.75	15.189	713.9
	Patients with PTH > 1000 pg	9	114.53	9.182	964.1
PTH level after therapy	Patients with PTH 180-300 pg / ml	15	98.00	10.488	123.1
	Patients with PTH 301-600 pg/ml	13	107.00	12.547	249.4
	Patients with PTH 180-300 pg / ml	20	105.18	9.223	650.7
	Patients with PTH > 1000 pg/ml	2	80.75	7.808	540.5

F (3, 156) = 106.034; p<0.001; kvad square = 0.67 (PTH I,II,III group)**;** F (3.156) = 55.434; p<0.001; kvad square = 0.51 (PTH IV group)

An additional Pearson Corerration analysis of the results was carried out, confirming the statistical significance of the Ca-P ratio and the PTH value, which is based on the Fisher Z-transformation (Table 6.)

Table 7 Pearson correlation statistical **significance analysis (Power Analysis - Pearson Correlation)**

Power Analysis Table						
	N	**Actual Powerb**	**Test Assumptions**			
			Power	**Null**	**Alternative**	**Sig.**
Pearson Correlationa	4	0.060	0.05	0.0	0.5	0.05

a. Two-sided test; b. based on Fisher's z-transformation and normal approximation with bias adjustment.

4. Discussion

Studies conducted in patients with end-stage renal disease and secondary hyperparathyroidism on hemodialysis show that demographic and baseline characteristics were representative for the hemodialysis population of patients with secondary hyperparathyroidism. The reduction in baseline of PTH values in patients treated with Paricalcitol was: II 36%, II 30.5%, III 9% and Cinacalcet-treated patients by 44%. The greatest decrease of value in PTH was observed in patients treated with Cinacalet for secondary hypeparathyroidism. In addition to a significant decrease in PTH, a significant decrease in serum calcium and phosphorus (Ca x P) and calcium and phosphorus multiples was observed in the Cinacalcet group. Approximately 62% of Cinacalcet-treated patients achieved a ≥ 56% reduction in PTH and this effect was consistent regardless of baseline of PTH.

According to Massry et al. elevated PTH levels reduce insulin secretion from the pancreas due to impaired calcium homeostasis, which further exacerbates glucose homeostasis. In a multicentre cross-sectional study, they investigated the prevalence of SHPT in patients with and without diabetes on a chronic hemodialysis program. The results showed that the prevalence of SHPT among the groups was similar[10].

In the study of Günther et al. in which the relation between PTH, vitamin D, renal insufficiency and cardiovascular diseases was investigated, it was concluded that elevated PTH is associated with a higher frequency of cardiovascular diseases and is an important risk factor for cardiovascular diseases. By increasing the serum values of PTH in patients with end-stage renal disease, the concentration of cytoplasmic calcium in the smooth muscle cells of the blood vessels increases, thereby results with the contraction of blood vessels[11].

Conigrave et al conducted a study in Japan and found that underlying kidney disease had no significant effect on PTH values[12].

In the examined study, with regard to gender representation, significant differences between the genders were found in favor of the male gender, while the analysis of searches by age showed a statistically significant difference only in value.

In the study Quitter et al. higher risk of death was related to PTH values of 900 pg/mL or more[13].

Unlike the previous study, we could not find a link in our study between the increased risk of mortality and the value of PTH, as we lacked data on the causes of death of our patients. It indicates the risk of calcification of blood vessels and soft tissues. The elevated values may be due to increased calcium intake, intake of phosphorus binders or increased calcium concentration in dialysate, as well as the effect of PTH on the bone itself.

Persistent hypercalcaemia and / or increased Ca × P product were observed more in the Paricalcitol group than in the Cinacalcet group. The difference in the incidence of hyperphosphatemia and hypercalcemia and/or elevated Ca × P product between the analysis is an interesting observation and may reflect the peculiarities of treatment in a single center. The importance of finding hypercalcemia and/or elevated Ca × P product is additionally important given that the development of hypercalcemia is more likely to occur when PTH levels are rapidly lowered and/or suppressed to levels below those considered therapeutic. In this regard, recent long-term studies have shown that Paricalcitol dosed in proportion may be effective in suppressing PTH at moderately elevated values, but may lead to hypercalcemia.

Results in this study found that phosphate levels in serum were relatively higher in the Paricalcitol groups than in the Cinacalcet groups, but there was no significant difference. There is an increasing risk of mortality with increasing levels of serum phosphate. In certain included studies, average levels of phosphate in serum of Paricalcitol or Cinacalcet were

above the upper limit of normal at the end of follow-up. In other words, both drugs are associated with a risk of causing hyperphosphatemia.

In our study, 87% of patients had elevated Ca and P values with PTH values. In the great American study Sun et al. during eight-year period, which monitored the values of calcium, phosphorus, PTH and alkaline phosphatase in 106.760 dialysed patients, the same correlation of calcium and PTH was found with the same explanation[13].

In the meta-analytical study of Chertow et al. Administration of Cinacalcet significantly reduced Ca in serum, and normalization of Ca levels was achieved in almost 90% of patients. A decrease in Ca is accompanied by an increase in phosphate levels indicating that Cinacalcet treatment may restore normal Ca homeostasis[14].

Silverberg et al.noticed that the greatest reduction in serum of Ca was in patients with higher baseline Ca levels[15]. Our study agrees with Silverberg et al. where a higher treatment effect was observed for higher Ca baseline values in serum. For these patients, Cinacalcet is a reasonable option in a treatment regimen for the purpose of controlling hypercalcemia. It has also been found that age and gender do not alter the effectiveness of Cinacalcet treatment.

It is important that the use of Cinacalcet does not guarantee the success of the treatment of hypercalcemia, although there are cases of spontaneous remission of SHPT reported by Nakao in his study. As for side effects of Cinacalcet, reported cases are relatively small. In the study, most side effects were classified as mild to moderate in severity and were relatively rare, resulting in withdrawal from treatment. Nausea or vomiting were the most commonly reported unwanted events, occurring in 23% of the antiemetic-treatable population studied. However, it should be taken into account avoiding of medicinal products that may prolong the QT interval in conditions of possible hypocalcaemia. Hypocalcemia after Cinacalcet is generally mild and asymptomatic, and Cinacalcet dose adjustments are generally sufficient to prevent severe hypocalcemia, according to Nakao[16].

Cinacalcet-based therapy effectively prevented hypercalcemia, more than half of the patients in the Cinacalcet group experienced hypocalcemia during the evaluation period. In contrast, hypercalcaemia, a common side effect of non-selective VDR activators, occurred in only 7.7% of subjects receiving Paricalcitol iv. and it did not occur in the group that was taking orally Paricalcitol. These findings are consistent with those observed in previous randomized controlled trials of iv. and oral Paricalcitol in hemodialysis patients that demonstrate effective PTH reduction without significantly increasing the risk of hypercalcemia when used within specified dose ranges.

There are also conflicting studies such as Cozzolin's study. These findings demonstrated the overall superiority of Paricalcitol over Cinacalcet in achieving the target levels of PTH. However, what is limiting is that the PTH values in which Paricalcitol was used compared to cinacalcet are not sufficiently reported[17].

In this study, a statistically significant relation between PTH and phosphate values was found,and also the presence of hyperphosphatemia in SHPT was noticed as well. In addition, in the available medical histories, there is insufficient information about the patient's dietary and other lifestyle habits, and their discipline during taking of medication therapy. A very important factor is the nutrition of the patient.

Protein intake should be strictly limited as patients undergoing dialysis for several years also have significant disorders of PTH and vitamin D. Taking into account all possible limitations and the results obtained, it is concluded that this area deserves further research[18].

5. Conclusion

Bone mineral metabolism disorders significantly contribute to a high risk of disease and mortality in patients with CKD. More and more drugs that can be used in prevention and treatment. It remains questionable whether new forms of SHPT treatment reduce the risk of clinical events of interest to patient survival, primarily affecting morbidity and mortality from cardiovascular disease.

Guidelines for the control of PTH, Ca and P values in patients on a chronic hemodialysis program, who suffer from SHPT:

- Hyperphosphatemia therapy (phosphate-poor diet, medicamentous therapy-sevelamer)
- Do not use dialysate with a concentration of Ca > 1.5 mmol/l.
- At extremely elevated phosphate levels, increase the number of dialysis.

- Cinacalcet therapy with or without vitamin D with PTH values greater than 800pg. The recommended starting dose of Cinacalcet for adults is 30 mg 2x per day. During dose titration, serum calcium levels should be monitored within 7 days. Pause taking of Cinacalcet if Ca is below 1.9 mmol / l. After correction with vitamin D, return to the minimum dose of Cinacalcet.
- At elevations of PTH from 181 to 799pg, Paricalcitol is given in doses as follows: PTH 181 – 300pg 1x1 ampoules of 5microgram iv. or 2x1 tablets of 2microgram orally, PTH 301 – 800PG give a 2x1 ampoule of 5 micrograms iv. or 2x2 tablets of 2 micrograms orally. In case of reduction of PTH by more than 60% reduce the dose of Paricalcitol by 2-4 micrograms. In case of increased PTH, switch to Cinacalcet therapy. If Ca is greater than 2.58 mmol/l or P is greater than 2.1 mmol/l or their product is greater than 5.5, pause with Paricalcitol therapy until Serum Ca and P are corrected.
- If the PTH value is 4 or more times above the upper limit of normal values, PTH values should be determined every 2 months)
- Serum PTH values may vary and treatment measures should focus on reducing the value of this hormone in dialysed patients to improve survival while controlling calcium and phosphorus levels.

Compliance with ethical standards

Disclosure of conflict of interest

All authors of the manuscript have no conflict of interests to declare.

Statement of ethical approval

The Present Research Work Does Not Contain Any Studies Performed On Animals / Humans Subjects by Any Of The Authors.

Statement of informed consent

No information about any individuals.

References

[1] Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol. 2011, 6(4):913-921. doi: 10.2215/CJN.06040710.

[2] Thadhani R. et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA. 2012, 307(7):674-684. doi: 10.1001/jama.2012.120.

[3] Owen WF Jr. Patterns of care for patients with chronic kidney disease in the United States: dying for improvement. J Am Soc Nephrol. 2003, 14(2):76-80. doi: 10.1097/01.asn.0000070145.00225.ec.

[4] Xu W, Gong L, Lu J, Tang W. Paricalcitol vs. Cinacalcet for secondary hyperparathyroidism in chronic kidney disease: A meta-analysis. Exp Ther Med. 2020, 20 (4): 3237-3243. doi: 10.3892 / etm.2020.9044.

[5] Orly L. Mineral-bone disorders in chronic renal disease medicine fluuminensis. Kidney Int. 2010, 46: 463-470.3-470.

[6] Crncevic Z, Pavlovic D, Zaputovic L. Bone mineral densitometry in patients on hemodialysis: difference between genders and what to measure. Ren Fail. 2010, 32 (3): 300-308. doi: 10.3109 / 08860221003611661.

[7] Chin YH, Tan MHQ, Ng JX, Yang SP, Kiew JJ, Khoo CM. Cinacalcet and primary hyperparathyroidism: systematic review and meta regression. Endocr Connect. 2020, 9 (7): 724-735. doi: 10.1530 / EC-20-0221.

[8] Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res. 2011, 109 (6): 697-711. doi: 10.1161 / CIRCRESAHA.110.234914.

[9] Lederer E. Regulation of serum phosphate. J Physiol. 2014, 592 (18): 3985-95. doi: 10.1113/jphysiol.2014.273979.

[10] Günther T, et al. Genetic ablation of parathyroid glands reveals another source of parathyroid hormone. Nature. 2000, 406 (6792): 199-203. doi: 10.1038/35018111.

[11] Conigrave AD. The Calcium-Sensing Receptor and the Parathyroid: Past, Present, Future. Front Physiol. 2016, 7: 563. doi: 10.3389 / fphys.2016.00563.

[12] Quitter U, Hoffmann M, Freichel M, Lohse MJ. Paradoxical block of parathormone secretion is mediated by increased activity of G alpha subunits. J Biol Chem. 2001, 276 (9): 6763-6769. doi: 10.1074 / jbc.M007727200.

[13] Sun Y, et al. Efficacy and safety of Cinacalcet compared with other treatments for secondary hyperparathyroidism in patients with chronic kidney disease or end-stage renal disease: a meta-analysis. Nephrol. 2020, 316 (3) 134-136. doi.org/10.1186/s12882-019-1639-9

[14] Chertow M, Cinacalcet Hydrochloride (Sensipar) in Hemodialysis Patients on Active Vitamin D Derivatives with Controlled PTH and Elevated Calcium × Phosphate. Clinical Journal of the American Society of Nephrology. 2006, 1 (2): 305-312. doi: 10.2215 / CJN.00870805

[15] Silverberg SJ, Bilezikian JP. Incipient primary hyperparathyroidism: a form of fruse of an old disease. J Clin Endocrinol Metab. 2003, 88 (11): 5348-52. doi: 10.1210 / jc.2003-031014.

[16] Nakao Y, Koike T, Ohta Y, Manaka T, Imai Y, Takaoka K. Parathyroid hormone boosts bone morphogenetic protein activity by increasing intracellular 3', 5 ' -cyclic adenosine monophosphate accumulation in osteoblastic MC3T3-E1 cells. Bone. 2009, 44 (5): 872-7. doi: 10.1016 / j.bone.2009.01.370.

[17] Cozzolino M, Galassi A, Conte F, Mangano M, Di Lullo L, Bellasi A. Treatment of secondary hyperparathyroidism: the clinical utility of etelcalcetide. Ther Clin Risk Manag. 2017, 13: 679-689. doi: 10.2147 / TCRM.S108490.

[18] Tägil M. et al.. Intermittent PTH (1-34) does not increase union rates in open rat femoral fractures and exhibits attenuated anabolic effects compared to closed fractures. Bone. 2010, 46 (3): 852-859. doi: 10.1016 / j.bone.2009.11.009.