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Original Article

A Retrospective Comparison of Treatment Options in Secondary Hyperparathyroidism on Calcium Metabolism: A Single Center Study

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Abstract

Background: Many patients on hemodialysis (HD) receive treatment for secondary hyperparathyroidism (sHPT), but few studies have assessed the clinical outcomes for these patients when treated with cinacalcet or parathyroidectomy (PTx). This study aimed to compare the short-term outcomes of cinacalcet and PTx in HD patients with sHPT.

Methods: The study included retrospective data from 52 patients with ESRD who underwent HD and were diagnosed with sHPT between 2001 and 2013. Data regarding participant age, gender, serum calcium (mg/dL), phosphorus (mg/dL), and parathormone (PTH, pg/mL) levels before and six months after treatment initiation (after surgery for patients who underwent PTx) were obtained from patient files.

Results: The study involved 12 patients who underwent PTx, 18 patients treated with cinacalcet, and 22 who received calcitriol. PTx was the only treatment that significantly reduced post-treatment calcium. The mean calcium levels of patients treated with PTx were 7.67±0.95 mg/dL, showing a mean difference of 1.2 mg/dL (p=0.005, paired-samples t-test). Both PTx and cinacalcet significantly reduced phosphorus levels, when compared in mean changes, patients who underwent PTx had higher median reductions in phosphorus concentrations compared to patients treated with cinacalcet (p=0.03, Mann-Whitney U test). Post-treatment PTH levels significantly decreased in both the PTx and cinacalcet groups, however, only the patients who underwent PTx achieved PTH levels within the recommended range; post-treatment PTH levels in the cinacalcet group remained higher than recommended levels.

Conclusion: Both PTx and cinacalcet are beneficial in managing sHPT, however, PTx provides more significant improvements in mineral metabolism, while cinacalcet offers a less invasive alternative as a medical treatment.

Keywords: Cinacalcet, Hyperparathyroidism, Parathyroidectomy, End-Stage Kidney Disease, Mineral and Bone Disorder

INTRODUCTION

End-stage renal disease (ESRD) is an increasing global health issue, affecting over 2 million people worldwide who require renal replacement therapies (RRT), such as hemodialysis (HD), peritoneal dialysis, or kidney transplantation (1). HD is the most common treatment for ESRD, especially in settings where other options are limited (2). Secondary hyperparathyroidism (sHPT) is a frequent complication among patients undergoing HD. sHPT is marked by increased levels of parathyroid hormone (PTH), which can cause bone mineral metabolism disorders resulting in hypercalcemia, hyperphosphatemia, elevated levels of FGF23, and a deficiency in active vitamin D. sHPT can contribute to negative cardiovascular and bone mineral outcomes (3,4). Epidemiological data in dialysis patients provide substantial evidence that elevated PTH is associated with mortality (5). According to the KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), the current recommendation for the management of sHPT includes

lowering serum phosphate levels through dietary phosphorus restriction and oral phosphorus binders, as well as controlling PTH levels through the use of vitamin D analogs and calcimimetic (4).

Calcimimetic agents, such as cinacalcet and etelcalcetide, have emerged as effective treatments for managing sHPT in HD patients. These agents activate calcium-sensing receptors in the parathyroid glands, reducing PTH secretion without increasing serum calcium and phosphorus levels (6,7). Parathyroidectomy (PTx) can serve as salvage therapy in sHPT that does not respond to medical treatments, including vitamin D, phosphorus-binding agents, and calcimimetics (4). Although calcimimetics targeting abnormal CKD-MBD parameters do not reduce cardiovascular mortality, they reduce PTH, calcium, and phosphorus levels and increase bone mineral density (7-9). Whereas, in addition to these positive effects, PTx may provide benefit on patient mortality (10,11). In contrast, PTx for sHPT in ESRD has been shown to have a higher complication and mortality rate compared to PTx for other indications (12). Therefore, surgery is typically reserved for patients with refractory disease that cannot be managed through medical therapy, even though there are reported cardiovascular benefits. Cinacalcet has proven effective for patients with advanced parathyroid hyperplasia, and since its introduction in many countries, the annual rates of PTx have decreased (13).

Many patients on HD receive treatment for sHPT, but few studies have assessed the clinical outcomes for these patients when treated with cinacalcet or PTx. This study aimed to compare the short-term outcomes of cinacalcet and PTx in HD patients with sHPT.

METHODS

Study Design and Population

The study included retrospective data from 52 patients with ESRD who underwent HD and were diagnosed with sHPT between 2001 and 2013. Patients were age and gender-matched and categorized into three groups based on their treatment options: Group 1 comprised patients who underwent PTx, Group 2 comprised patients treated with cinacalcet, and Group 3 comprised patients who received calcitriol (control group). Patients who had previously undergone thyroid or parathyroid surgery and received cinacalcet/etelcalcetide treatment before follow-up, could not receive effective HD treatment for any reason, and had insufficient data were excluded from the study. In addition, patients under 18 and those with active infections or malignancies were excluded from the study.

Data Collection and Processing

Data regarding participant age, gender, serum calcium (mg/dL), phosphorus (mg/dL), and parathormone (PTH, pg/mL) levels before and six months after treatment initiation (after surgery for patients who underwent PTx) were obtained from patient files. All assays were performed on blood samples prior to HD. Plasma PTH was measured using an immunometric assay that detects full-length and amino-terminally truncated peptide fragments (normal range 12–72 pg/mL). As recommended in the literature, appropriate PTH levels in HD patients were defined as being maintained within a range of approximately 2 to 9 times the upper normal limit for the assay (upper limit 378 pg/mL) (14). The inclusion criteria for the cinacalcet and PTx groups were plasma PTH level above the upper limit of 378 pg/mL, serum calcium-phosphate product above 45 mg2/dL2, and serum calcium above 8.4 mg/dL (7,14). All patients received HD treatment three days a week, and their HD treatments were similar. The patients' last three-month kt/V values were above 1.2. All patients followed an appropriate diet and received phosphorus-lowering treatment for phosphorus control. All patients, including the calcitriol control group, received treatment with at least three mcg/week of calcitriol. Under appropriate calcitriol treatment, PTH levels were above 1000 pg/mL in the PTx group. For patients receiving cinacalcet, treatment began at a low dose, as recommended in the literature, and was gradually increased to the maximum dose based on calcium levels (7).

Ethical Considerations

This study was carried out according to the ethical rules and principles of the Declaration of Helsinki. All participants were informed of the study protocol and provided informed consent, and patient data was retrospectively accessed and anonymized before analysis. The retrospective study protocol was approved by the local Hospital's ethics committee (Date: 01/2014, protocol number: 17).

STATISTICAL ANALYSIS

Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 programs were used for statistical analysis. The normality of continuous variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical data were presented as counts and percentages, while continuous variables were reported as means and standard deviations. Categorical comparisons were analyzed using Pearson's chi-square test and Fisher's exact test. For continuous variables, one-way analysis of variance (ANOVA) was used to compare more than two groups. Post-hoc analysis was conducted using Tukey's HSD and Tamhane's T2 tests. Comparisons between the two groups were conducted using t-tests and Mann-Whitney U tests. A statistical significance level of 0.05 was established for the study.

RESULTS

The study involved 12 patients who had PTx, 18 patients

treated with cinacalcet, and 22 who received calcitriol. All patients were matched for age and sex, had ESRD, were undergoing HD, and were diagnosed with sHPT. Twenty-six patients (50%) were female; 5 (41.7%) patients had PTx; 9 (50%) patients were treated with cinacalcet, and 12 (54.5%) who received calcitriol were female. Gender distribution was similar among groups (p=0.773, chi-square test). The mean age of patients undergoing PTx was 58.2±12.1 years, compared to 55.3±10.4 years for those treated with cinacalcet, and 58.3±16.5 years for those treated with calcitriol. The mean ages of the three groups were similar (p=0.775, one-way ANOVA).

The mean pre-treatment calcium levels for patients undergoing PTx were 8.87±0.76 mg/dL. In comparison, patients treated with cinacalcet had mean levels of 8.98±0.57 mg/dL, while those treated with calcitriol had mean levels of 8.54±0.59 mg/dL. Overall, the pre-treatment calcium levels among the three groups were similar (p=0.07, one-way ANOVA). PTx was the only treatment that significantly reduced post-treatment calcium levels. The mean calcium levels of patients treated with PTx were 7.67±0.95 mg/dL, showing a mean difference of 1.2 mg/dL (p=0.005, paired-samples t-test). In comparison, post-treatment mean calcium levels for patients treated with cinacalcet was 8.77±0.7 mg/dL (p=0.361, paired-samples t-test) and those treated with calcitriol had post-treatment mean calcium levels of 8.59±0.54 mg/dL (p=0.672, paired-samples t-test) (**Figure 1A, B, C**).

The mean pre-treatment phosphorus levels for patients undergoing PTx were 6.57±0.98 mg/dL. In comparison, patients treated with cinacalcet had mean levels of 5.91±1.45 mg/dL, while those treated with calcitriol had mean levels of 5.19±1.31 mg/dL. Pre-treatment phosphorus levels between the three groups differed significantly (p=0.015, one-way ANOVA), specifically, patients undergoing PTx had higher phosphorus levels compared to those treated with calcitriol (p=0.013, post-hoc Tukey's HSD); other two-groups comparisons were similar. Both PTx and cinacalcet significantly reduced phosphorus levels. After treatment, the phosphorus levels of patients who underwent PTx were measured at 4.5±1.26 mg/dL (p=0.001, paired-samples t-test), while those treated with cinacalcet had levels of 4.82±1.35 mg/dL (p=0.004, paired-samples t-test). Calcitriol did not significantly change phosphorus levels, post-treatment phosphorus levels were 5.31±1.19 mg/dL (p=0.336, paired-samples t-test) (Figure 1B). When compared in mean changes, patients who underwent PTx had higher median reductions in phosphorus concentrations compared to patients treated with cinacalcet (p=0.03, Mann-Whitney U test).

The mean pre-treatment PTH levels for patients undergoing PTx were 1935.14±220 pg/mL. In comparison, patients treated with cinacalcet had mean PTH levels of 1254.22±670.58 pg/mL, while those treated with calcitriol had mean PTH levels of 261.05±167.68 pg/mL. There were significant differences in pre-treatment PTH levels among the three groups (p=0.001, one-way ANOVA). Specifically, patients undergoing PTx had higher PTH levels compared to those treated with cinacalcet (p=0.002, post-hoc Tukey's HSD) and calcitriol (p=0.001, post-hoc Tukey's HSD). Additionally, patients treated with cinacalcet also had higher PTH levels than those treated with calcitriol (p=0.001, post-hoc Tukey's HSD). Post-treatment PTH levels significantly decreased in both the PTx and cinacalcet groups. The mean PTH levels were 161.28±91.11 pg/mL for the PTx group and 488.89±

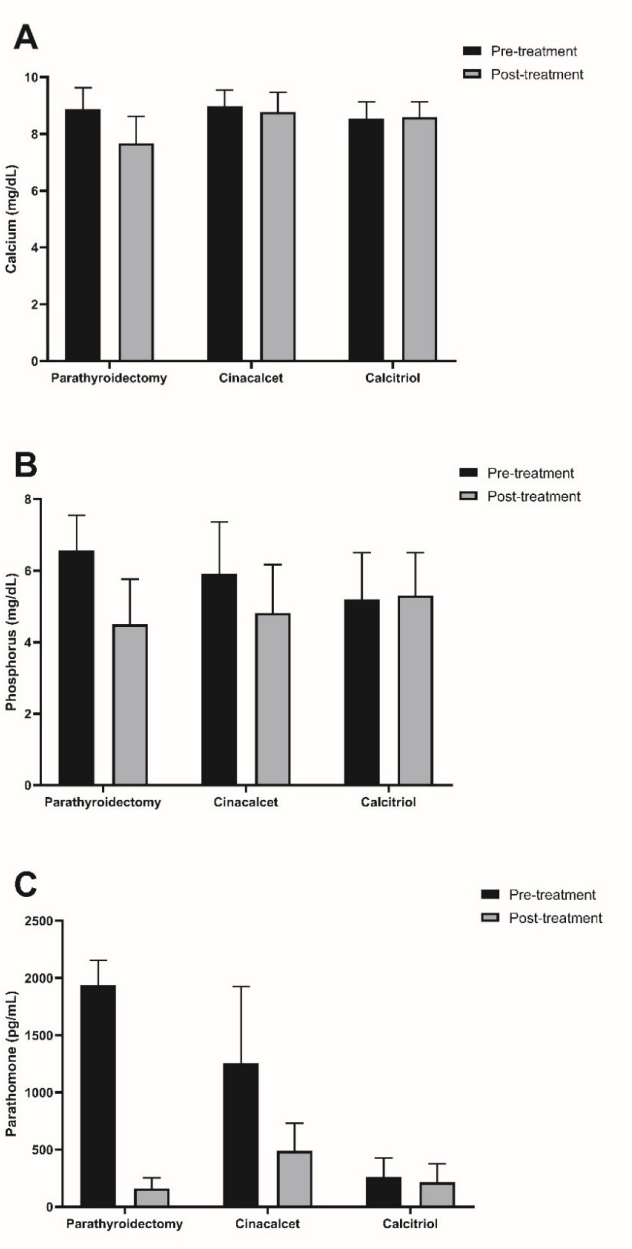

Figure 1. Pre- and post-treatment serum calcium (A), phosphorus (B) and parathormone (C) levels of three different treatment groups.

42.22 pg/mL for the cinacalcet group (p=0.001 for both comparisons, paired-samples t-test). In comparison, post-treatment PTH levels in patients treated with calcitriol remained similar to their pre-treatment levels, measuring 162.69±111.05 pg/mL (p=0.21, paired-samples t-test) (Figure 1C). Notably, only the patients who underwent PTx and those treated with calcitriol achieved PTH levels within the recommended range for ESRD. In contrast, post-treatment levels in patients treated with cinacalcet remained higher than the recommended levels. Post-treatment PTH levels differed significantly between three groups (p=0.001, one-way ANOVA); specifically, both patients underwent PTx (p=0.001, post-hoc Tamhane's T2) and patients treated with calcitriol (p=0.006, post-hoc Tamhane's T2) had lower PTH levels compared to patients treated with cinacalcet.

DISCUSSION

sHPT is one of the serious health problems frequently encountered in HD patients (15). Changes in calcium, phosphorus, and PTH metabolism in these patients are linked to morbidities, including bone pain, fractures, calciphylaxis, and, notably, an increased risk of cardiovascular issues and mortality (5,16). sHPT related to ESRD is typically managed with phosphorus-binding agents and active vitamin D. Nevertheless, achieving the desired levels of calcium, phosphorus, and PTH remains unattainable for many patients (10,17). This study examined the short-term outcomes of cinacalcet versus PTx in HD patients with sHPT. Our findings indicated that both treatment options were superior to calcitriol alone in managing CKD-MBD. Additionally, PTx was found to lower PTH levels more effectively, although it resulted in a higher prevalence of lower calcium levels.

PTx is frequently recommended as an effective treatment option in sHPT, especially in patients with advanced hyperplasia (12). However, surgical intervention carries the risk of complications and potential side effects; therefore, it is emphasized that it should be applied primarily to patients who are resistant to medical treatment (13). Our study's differences between the PTx and cinacalcet treatment groups were significant. PTx significantly reduced PTH, calcium, and phosphorus levels, supporting its effectiveness in managing sHPT. Cinacalcet stands out as a medical treatment for sHPT that can be preferred over surgical intervention; it inhibits PTH production by activating calcium-sensing receptors in the parathyroid glands, providing an effective approach to balancing patients' PTH levels (7). There is no strong evidence in the literature that cinacalcet reduces cardiovascular mortality; however, it is effective in correcting sHPT and CKD-MBD (18). Therefore, the effect of cinacalcet treatment may be limited, and PTx may be necessary in refractory patients (10). In our study, PTH levels of patients receiving cinacalcet decreased significantly after treatment but did not reach the targeted PTH range, unlike PTx. In addition, although significant improvement in phosphorus levels was observed after cinacalcet, this effect was more limited compared to PTx, which may lead to the conclusion that cinacalcet is potentially less effective than PTx and shows greater individual response differences.PTx is not without flaws regarding CKD-MBD; one of the important side effects of calcimimetics and PTx is hypocalcemia (18). Our study showed that cinacalcet did not significantly decrease calcium levels in our patients, whereas PTx did, with a 1.2 mg/dl decrease. Although the decrease was not life-threatening, patients treated with PTx should be monitored for hypocalcemia.

Limitations

Our study had some limitations. First, being a single-center investigation with a limited patient population may have weakened our statistical power. Second, as our research relied on data from electronic medical records, we faced challenges such as incomplete data and accessibility issues with laboratory results, often inherent to retrospective studies. Third, while the demographic data for the PTx and cinacalcet groups were similar, other unrecorded or unidentified factors—such as current medications and additional comorbidities—might have influenced the results. Fourth, there are no clear criteria in the literature for diagnosing sHPT in HD patients and for choosing calcimimetic/PTx treatments, and treatment decisions often vary from center to center. Nevertheless, we believe that these findings, which our center treated by setting certain standards and detecting as a result, may contribute to the literature. Finally, the short follow-up period prevented the evaluation of the patients in terms of morbidity and mortality. Studies with a larger number of patients and longer follow-up periods are necessary.

CONCLUSION

Our findings suggest that PTx and cinacalcet are beneficial in managing sHPT, but both treatment approaches have different advantages and limitations. PTx provides more significant improvements in mineral metabolism, while cinacalcet offers a less invasive alternative as a medical treatment. However, it should be noted that this is retrospective data, and treatment strategies should be personalized according to the patient's clinical condition, considering their responses to treatment and the risks of complications. This study's results allow us to understand better the effectiveness and limitations of different treatment methods for sHPT in HD patients. These findings are important for guiding treatment decisions, and future studies may provide more comprehensive data by examining long-term outcomes.

DECLARATIONS

Ethics committee approval: This study was carried out according to the ethical rules and principles of the Declaration of Helsinki. All participants were informed of the study protocol and provided informed consent, and patient data was retrospectively accessed and anonymized before analysis. The retrospective study protocol was approved by the local Hospital's ethics committee (Date: 01/2014, protocol number: 17).

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Conflicts of interest: Authors declare none.

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AI: Not applied

REFERENCES

1. Robinson BM, Akizawa T, Jager KJ, Kerr PG, Saran R, Pisoni RL. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet*. 2016;388(10041):294-306. doi:10.1016/S0140-6736(16)30448-2
2. Braun MM, Khayat M. Kidney Disease: End-Stage Renal Disease. *FP Essent*. 2021;509:26-32.
3. Floege J, Kim J, Ireland E, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant*. 2011;26(6):1948-1955. doi:10.1093/ndt/gfq219
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) [published correction appears in Kidney Int Suppl (2011). 2017 Dec;7(3):e1. doi: 10.1016/j.kisu.2017.10.001]. *Kidney Int Suppl (2011)*. 2017;7(1):1-59. doi:10.1016/j.kisu.2017.04.001
5. Tentori F, Wang M, Bieber BA, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. *Clin J Am Soc Nephrol*. 2015;10(1):98-109. doi:10.2215/CJN.12941213
6. Itano Y, Kato S, Tsuboi M, et al. A Prospective, Randomized Clinical Trial of Etelcalcetide in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism (the DUET Trial). *Kidney Int Rep*. 2020;5(12):2168-2177. Published 2020 Sep 18. doi:10.1016/j.ekir.2020.09.010
7. Parfrey PS, Chertow GM, Block GA, et al. The clinical course of treated hyperparathyroidism among patients receiving hemodialysis and the effect of cinacalcet: the EVOLVE trial. *J Clin Endocrinol Metab*. 2013;98(12):4834-4844. doi:10.1210/jc.2013-2975
8. EVOLVE Trial Investigators, Chertow GM, Block GA, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*. 2012;367(26):2482-2494. doi:10.1056/NEJMoa1205624
9. Eidman KE, Wetmore JB. Managing hyperparathyroidism in hemodialysis: role of etelcalcetide. *Int J Nephrol Renovasc Dis*. 2018;11:69-80. Published 2018 Feb 5. doi:10.2147/IJNRD.S128252
10. Komaba H, Hamano T, Fujii N, et al. Parathyroidectomy vs Cinacalcet Among Patients Undergoing Hemodialysis. *J Clin Endocrinol Metab*. 2022;107(7):2016-2025. doi:10.1210/clinem/dgac142
11. Alvarado L, Sharma N, Lerma R, et al. Parathyroidectomy Versus Cinacalcet for the Treatment of Secondary Hyperparathyroidism in Hemodialysis Patients. *World J Surg*. 2022;46(4):813-819. doi:10.1007/s00268-022-06439-7
12. Ishani A, Liu J, Wetmore JB, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. *Clin J Am Soc Nephrol*. 2015;10(1):90-97. doi:10.2215/CJN.03520414
13. Tominaga Y, Kakuta T, Yasunaga C, Nakamura M, Kadokura Y, Tahara H. Evaluation of Parathyroidectomy for Secondary and Tertiary Hyperparathyroidism by the Parathyroid Surgeons' Society of Japan. *Ther Apher Dial*. 2016;20(1):6-11. doi:10.1111/1744-9987.12352
14. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters [published correction appears in Kidney Int. 2017 Dec;92(6):1558. doi: 10.1016/j.kint.2017.10.001]. *Kidney Int*. 2017;92(1):26-36. doi:10.1016/j.kint.2017.04.006
15. Moe SM, Drüeke T, Lameire N, Eknoyan G. Chronic kidney disease-mineral-bone disorder: a new paradigm. *Adv Chronic Kidney Dis*. 2007;14(1):3-12. doi:10.1053/j.ackd.2006.10.005
16. Hruska KA, Choi ET, Memon I, Davis TK, Mathew S. Cardiovascular risk in chronic kidney disease (CKD): the CKD-mineral bone disorder (CKD-MBD). *Pediatr Nephrol*. 2010;25(4):769-778. doi:10.1007/s00467-009-1337-0
17. Komaba H, Tanaka M, Fukagawa M. Treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Intern Med*. 2008;47(11):989-994. doi:10.2169/internalmedicine.47.1051
18. Wang AY, Lo WK, Cheung SC, Tang TK, Yau YY, Lang BH. Parathyroidectomy versus oral cinacalcet on cardiovascular parameters in peritoneal dialysis patients with advanced secondary hyperparathyroidism (PROCEED): a randomized trial. *Nephrol Dial Transplant*. 2023;38(8):1823-1835. doi:10.1093/ndt/gfad043