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ORIGINAL ARTICLE

Combined Intravenous and Oral Calcimimetic Therapy for Secondary Hyperparathyroidism in Hemodialysis Patients Ineligible or Unwilling to Undergo Parathyroidectomy

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ABSTRACT

Introduction: Secondary hyperparathyroidism (SHPT) is a common and serious complication in chronic kidney disease patients on hemodialysis. For patients ineligible or unwilling to undergo parathyroidectomy, pharmacologic therapy with calcimimetics offers a non-surgical alternative.

Objective: To evaluate the effectiveness and safety of combining intravenous (IV) and oral calcimimetic therapy in managing SHPT in hemodialysis patients who are either ineligible or unwilling to undergo parathyroidectomy.

Methodology: This prospective study was conducted at Lahore general hospital during June 2021 to May 2022 and included 110 adult hemodialysis patients with uncontrolled SHPT. Patients were treated with a combination of IV etelcalcetide and oral cinacalcet for 24 weeks. Serum intact parathyroid hormone (iPTH), calcium, and phosphate levels were monitored at baseline, 12 weeks, and 24 weeks.

Results: Combined therapy significantly reduced mean iPTH levels from 980 ± 220 pg/mL at baseline to 480 ± 180 pg/mL at 24 weeks ($p < 0.001$). Serum calcium decreased from 9.4 ± 0.6 to 8.8 ± 0.5 mg/dL ($p = 0.01$), and phosphate levels declined modestly. 68% of patients achieved >30% reduction in iPTH. Gastrointestinal side effects occurred in 14%, mostly mild; hypocalcemia was reported in 9%.

Conclusion: Combined IV and oral calcimimetic therapy is effective in reducing iPTH levels and controlling biochemical parameters in SHPT patients on hemodialysis who cannot undergo parathyroidectomy. The regimen is well tolerated and provides a viable non-surgical management option.

Keywords: SHPT, hemodialysis, calcimimetics, etelcalcetide, cinacalcet

INTRODUCTION

SHPT is a commonly found and serious problem in the framework of chronic kidney disease in particular in the population of patients on maintenance hemodialysis[1]. Disruption of calcium, phosphate, and calcitriol regulation causes parathyroid hyperplasia and increased secretion of parathyroid hormone (PTH), characteristic of SHPT[2]. Persistent elevation of PTH contributes to high-turnover bone disease, predisposition to vascular calcification, increased cardiovascular risks, and increased mortality in ESRD-susceptible individuals. The efficient treatment of SHPT is irreplaceable in minimizing the medical complications of CKD-MBD and improve long-term effectiveness for patients[3-5]. Conventional therapy usually includes restricting dietary phosphate levels, the use of phosphate binders, and the administration of vitamin D analogs, but most patients find themselves requiring calcimimetic therapy to regulate PTH levels[6]. The calcimimetics increase the activity of the calcium-sensing receptor on parathyroid cells, which reduces PTH levels, but it is independent of calcium and phosphate levels. The first calcimimetics of choice in clinical use are cinacalcet, to be taken orally, and etelcalcetide, administered intravenously[7].

Cinacalcet, the first approved calcimimetic by FDA is famous for its massive success in reducing serum PTH, Ca, and phosphate in large studies[8]. Cinacalcet despite its efficacy is limited in clinical application because of common gastrointestinal side effects such as nausea and vomitting, as well as low patient compliance linked to daily oral intake[9]. A newer available option, etelcalcetide, which is given in intravenous infusions three times a week after dialysis leads to improved adherence and overall control of PTH. It has been associated with the alleviation of gastrointestinal-related problems although it increases the risk of asymptomatic hypocalcemia. While these drugs are effective in their own right, single-agent calcimimetics are not regularly successful in producing the effect, especially in patients with severe disease or high-dose intolerances[10]. The combination of oral and intravenous calcimimetic therapy provides a good approach to the treatment of patients unsuitable for parathyroidectomy due to age, heart disease, or refusal to undergo surgery. Current evidence, with its shortcomings, suggests that the use of oral as well as intravenous calcimimetics has the potential to be superior to monotherapy in reaching target levels of PTH and stabilizing the mineral balance. Some initial datasets and clinical case studies have revealed encouraging biochemical outcomes as well as good tolerability for these patients while substantial clinical evidence is lacking, particularly in patients who are unresponsive or unable to tolerate conventional therapies and who do not meet surgical eligibility[11].

Objectives: This study aims to evaluate the clinical outcomes of combined intravenous and oral calcimimetic therapy in hemodialysis patients with SHPT who are not candidates for parathyroidectomy.

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METHODOLOGY

This prospective observational study was conducted at Lahore General Hospital during June 2021 to May 2022 and included 110 adult patients undergoing maintenance hemodialysis with persistent secondary hyperparathyroidism (SHPT). Patients were treated with a combination of intravenous calcimimetic and oral cinacalcet over a 24-week period.

Inclusion Criteria:

- Adults aged ≥18 years on thrice-weekly hemodialysis for ≥6 months
- Serum intact parathyroid hormone (iPTH) >800 pg/mL at baseline
- Ineligible for parathyroidectomy due to comorbidities
- Ability to comply with oral and intravenous medication schedules

Exclusion Criteria:

- Recent parathyroidectomy (within the past 6 months)
- Ongoing malignancy or active infection

- Severe gastrointestinal disorders affecting oral drug absorption
- Serum calcium <7.5 mg/dL or >11.0 mg/dL at baseline
- Known allergy or intolerance to calcimimetic agents

Data Collection: Demographic data (age, sex, dialysis duration, comorbidities) were recorded at baseline. Biochemical parameters including iPTH, corrected serum calcium, and phosphate were measured at three-time points: baseline, 12 weeks, and 24 weeks. Intravenous calcimimetic was initiated at 2.5–5 mg three times weekly post-dialysis and titrated up to a maximum of 10 mg based on response and tolerability. Oral cinacalcet was started at 30 mg/day and increased as needed to a maximum of 60 mg/day. Dose adjustments of phosphate binders and vitamin D analogs were recorded when applicable. Adverse events, treatment interruptions, and oral medication adherence were monitored and documented throughout the study duration.

Statistical Analysis: Statistical analysis was performed using SPSS version 17. Descriptive statistics including means, standard deviations, and percentages were used to summarize baseline characteristics and outcomes. Paired t-tests were applied to compare changes in iPTH, calcium, and phosphate levels at baseline and follow-up visits. A p-value <0.05 was considered statistically significant for all comparisons.

RESULTS

The study included 110 hemodialysis patients with an average age of 56.8± 11.2 years; 62% were male. The average duration on dialysis was 5.6± 3.2 years, and nearly half of the patients (48%) had diabetes. The mean baseline iPTH level was very high at 980 pg/mL, with calcium at 9.4± 0.6 mg/dL and phosphate at 5.8± 0.7 mg/dL. When stratified, those who responded to therapy (68% of patients) had slightly lower baseline phosphate and calcium, but differences were not statistically significant (p > 0.05), indicating comparable baseline characteristics across subgroups.

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Total (n=110)	Etel + Cinacalcet Responsive (n=75)	Etel + Cinacalcet Non-responsive (n=35)	p-value
Mean Age (years)	56.8 ± 11.2	55.9 ± 10.9	58.5 ± 11.7	0.41
Male (%)	62% (68/110)	60% (45/75)	65.7% (23/35)	0.62
Duration of Dialysis (years)	5.6 ± 3.2	5.4 ± 3.1	6.0 ± 3.4	0.29
Diabetes Mellitus (%)	48% (53/110)	50% (38/75)	42.9% (15/35)	0.48
Baseline iPTH (pg/mL)	980 ± 220	978 ± 218	985 ± 225	0.87
Baseline Calcium (mg/dL)	9.4 ± 0.6	9.3 ± 0.5	9.5 ± 0.7	0.33
Baseline Phosphate (mg/dL)	5.8 ± 0.7	5.7 ± 0.6	5.9 ± 0.8	0.45

Biochemical monitoring showed a substantial decrease in mean iPTH levels from 980± 220 pg/mL at baseline to 640± 210 pg/mL at 12 weeks and 480± 180 pg/mL by 24 weeks (p < 0.001). Serum calcium levels decreased slightly from 9.4± 0.6 to 8.8± 0.5 mg/dL (p = 0.01), and phosphate levels declined from 5.8± 0.7 to 5.1± 0.5 mg/dL (p = 0.03).

Table 2: Biochemical Changes Over Time

Parameter	Baseline	Week 12	Week 24	Mean Change	p-value
iPTH (pg/mL)	980 ± 220	640 ± 210	480 ± 180	–500 ± 190	<0.001
Corrected Calcium (mg/dL)	9.4 ± 0.6	9.0 ± 0.5	8.8 ± 0.5	–0.6 ± 0.3	0.01
Phosphate (mg/dL)	5.8 ± 0.7	5.4 ± 0.6	5.1 ± 0.5	–0.7 ± 0.3	0.03

68% (75 patients) achieved at least a 30% reduction in iPTH levels, and 42% (46 patients) achieved a 50% reduction. Additionally, 53% of patients (58 individuals) attained a target iPTH level of less than 600 pg/mL by week 24. Among these responders, mean post-treatment iPTH was around 470 pg/mL. Hypocalcemia occurred in 8–11% of patients in these response categories, suggesting that while effective, the regimen requires calcium monitoring.

Table 3: iPTH Reduction Targets Achieved

Reduction Threshold	Number of Patients	Percentage of Total (%)	Mean iPTH at 24 Weeks (pg/mL)	Associated Hypocalcemia (%)
≥30% Reduction	75	68.2%	470 ± 160	8%
≥50% Reduction	46	41.8%	420 ± 140	11%
iPTH <600 pg/mL	58	52.7%	440 ± 150	9%

The majority of patients (87.3%) were fully compliant with both IV and oral medications. About 9% missed fewer than 10% of their oral doses, mostly due to mild GI discomfort. A small group (4 patients; 3.6%) missed 10% or more of doses, often due to non-adherence.

Table 4: Compliance and Persistence

Compliance Group	Patients (n)	Percentage (%)	Reason for Missed Doses	Effect on iPTH Response
Fully Compliant	96	87.3%	-	High
Missed <10% of Doses	10	9.1%	GI side effects	Moderate
Missed ≥10% of Doses	4	3.6%	Non-adherence	Low

DISCUSSION

The assessment considered the effect and tolerability of giving calcimimetic intravenously and clinically. Pairing these two calcimimetics has been found by the study to bring about marked improvements of principal biochemical parameters and success in reaching guideline-set iPTH targets in a significant number of patients. The study subjects at the onset were selected to have severe SHPT, with a mean IPTH concentration of 980 pg/ML. Over the 24 weeks of treatment, participants reported a significant decline in iPTH levels to 480 pg/mL with a mean reduction of 500 pg/mL (p < 0.001). The clinical relevance of this outcome is clear, as 68% experienced ≥30% decline of iPTH and 53% obtained iPTH in <600 pg/mL[12]. Serum calcium and phosphate levels also improved modestly but significantly with values falling to 8.8 mg/dL from 9.4 (p = 0.01) and to 5.1 mg/dL from 5.8 (p = 0.03). This result points to the working principle of calcimimetics, which enhances the sensitivity of the calcium-sensing receptor and weakens the PTH-triggered release of calcium and phosphate. As recently as in the previous investigation, it has been found that it is beneficial to treat patients with comorbidities and low SHPT response to cinacalcet with etelcalcetide with beneficial adjustments in mineral metabolism Overall the combination therapy reported good tolerability[13]. Gastrointestinal symptoms (commonly reported with cinacalcet) affected 13.6% of patients, with 9.1% of them suffering from hypocalcemia (both conditions were in general mild and non-

operated). Adverse events caused discontinuation of therapy in only 3.6% of patients[14]. This is consistent with prior studies that show that alone use of cinacalcet may cause up to 20-30% of patients to suffer nausea and vomiting, whereas etelcalcetide alone is correlated with a greater prevalence of asymptomatic hypocalcemia. Lower amounts of both medications in combination with each other may be able to serve to reduce the side effects while still being fairly efficacious[15]. Adjustments in withdrawals of supportive treatments were expected and an everyday occurrence. Over a third (32%) of subjects had to increase their dosage of phosphate binders, while 25% were diagnosed with an increase in vitamin D analog medications they take[16]. These changes echo earlier clinical observations, stressing the importance of individualized, responsive adjustments in calcimimetic therapy, as well as the restoration of calcium-phosphorus equilibrium and limitation of treatment variability. The percentage of 100% compliant patients was also high, at 87.3% showing compliance in oral and IV therapy. Under the high rate of compliance, it is reasonable to attribute the positive results to compliance. In the past, poor adherence has been regarded as a major issue in treating SHPT where treatment is entirely by oral preparations[17]. Including IV etelcalcetide at each dialysis session facilitates the steady release of the drug and may increase patient compliance with treatment if co-administered with other treatment regimens[18]. Notwithstanding encouraging results, the study has several limitations. The absence of randomness, and lack of a comparator in such a study weakens the estimation of efficacy of combined therapy and that of the treatment where only one of the medications is used. Although the research showed promising changes in its biochemical parameters, it could not address cardinal clinical endpoints such as cardiovascular results, bone turnover levels, or patient satisfaction in the quality of life. Based on these challenges, the economic implications of the integrated therapy should be well explored in future studies.

CONCLUSION

It is concluded that the combination of intravenous etelcalcetide and oral cinacalcet is an effective and well-tolerated treatment strategy for managing secondary hyperparathyroidism in hemodialysis patients who are ineligible or unwilling to undergo parathyroidectomy. Over 24 weeks, this dual approach led to significant reductions in serum iPTH levels and modest improvements in calcium and phosphate control. A majority of patients achieved guideline-recommended targets for iPTH reduction, with a favorable safety profile and high treatment adherence.

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