

Original Study

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Cinacalcet versus parathyroidectomy for primary hyperparathyroidism: a single centre experience

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Abstract

Background and Aim.

Parathyroidectomy is the standard treatment for primary hyperparathyroidism (PHPT). Cinacalcet, an allosteric modulator of the calcium sensing receptor, has been shown to be effective in reducing serum calcium levels and it has gained prominence as a non-invasive treatment in PHPT. Aim of the study was to compare the efficacy and tolerability of medical therapy vs surgery in a cohort of PHPT patients.

Patients and Methods.

The study included 63 consecutive subjects (14 men and 49 women, median age 62.4 ± 12 yr) with PHPT: 50 subjects (40 F and 10 M, ratio F/M 4:1; median age 59.6 ± 16.6 years, range 37-82) underwent parathyroidectomy, while 13 (9 F and 4 M, ratio F/M 2.5:1, median age 76.5 ± 6.2 years, range 64-83), who were ineligible for surgery, were treated with cinacalcet. Cinacalcet was administered at increasing dosages until normal serum calcium was reached or side effects occurred. Serum calcium and PTH was measured and adverse events were monitored during a 12 month-duration follow-up.

Results.

All patients who had undergone parathyroidectomy normalized both serum calcium and PTH levels after surgery ($P=0.001$ vs baseline) and none of them experienced persistent and/or recurrent PHPT during follow-up. In the group under cinacalcet therapy, serum calcium significantly decreased in all patients within 4 weeks ($P = 0.01$ vs baseline) and normalized in all patients at prolonged follow-up ($P=0.001$ vs baseline), while PTH slightly decreased during follow-up ($P=0.878$ vs baseline) and never reached a normal value.

Conclusion.

Surgical treatment is curative and safe in most cases of PHPT. Cinacalcet represents an effective therapeutic option, from the perspective of hypercalcemia improvement, in PHPT patients who have contraindications to surgery or persistent PHPT after surgery.

KeyWords: cinacalcet;parathyroidectomy; primary hyperparathyroidism; hypercalcemia.

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Introduction

Primary hyperparathyroidism (PHPT) is characterised by elevated secretion of parathyroid hormone (PTH) leading to hypercalcaemia (1). Its incidence increases with age especially in women, with a

prevalence of 21/1000 in women between 55 and 75 years-old, corresponding to 3/1000 in the general population, but it is the same in two sex before 45 years (2). PHPT is most often caused by a single adenoma (80 to 85%) or four-gland hyperplasia (10 to 15%), mainly occurs as a sporadic disease but it may be part of a hereditary syndrome, including multiple endocrine neoplasia (MEN) types 1, 2A, and 4, hyperparathyroidism-jaw tumor (HPT-JT) syndrome, familial isolated hyperparathyroidism, familial hypocalciuric hypercalcemia (FHH), and neonatal severe PHPT (3, 4). Although the disease is often asymptomatic, complications can be progressive and/or severe, including bone loss and fractures, kidney stones and gastrointestinal disturbances; symptoms such as muscle weakness, depression, and neuropsychiatric disturbance have also been reported.

Parathyroidectomy (PTx) is the therapeutic procedure able to cure the disease and has a success rate of up to 90–95% (5). Surgery should be considered in moderate-to-severe PHPT and in presence of symptoms of hypercalcemia or complications and should be advised in patients with asymptomatic PHPT who meet the criteria for surgery according to the latest international guidelines (6) About 5–12% of patients with PHPT may have persistent or recurrent PHPT after parathyroidectomy (7). Repeating surgery could be associated with increased incidence of complications, including recurrent laryngeal nerve damage or permanent hypoparathyroidism (8).

Patients with persistent PHPT after parathyroidectomy or with contraindications for surgery or patient who refuse undergoing operation have few treatment options currently available. Cinacalcet hydrochloride is an allosteric modulator of the calcium sensing receptor (CaSR) which is strongly expressed on the surface of parathyroid cells as well as in other tissues (9). Cinacalcet enhances the sensitivity of the CaSR to the prevailing extracellular calcium, resulting in an increase in the intracellular calcium concentration and a concomitant reduction in PTH released by the parathyroid gland. Cinacalcet reduces serum calcium and PTH levels in patients with mild PHPT compared with placebo (10) and significantly lowers serum calcium by greater than 1 mg/dl (0.25 mmol/liter) in more than 60% of patients with parathyroid cancer (11) and Multiple Endocrine Neoplasia type 1 (MEN 1) (12)

The present study was aimed at evaluating the effectiveness of cinacalcet in reducing serum calcium and PTH concentrations in PHPT patients ineligible for, or unwilling to undergo, surgery in comparison with PHPT patients who undergone PTx. Secondary objectives were to assess the safety of cinacalcet compared to surgery.

Patients and methods

Patients.

Sixty-three consecutive patients (14 men and 49 women, median age 62.4 ± 12 yr) diagnosed with PHPT at the Endocrine Unit of the University Hospital “AOU Policlinico G. Martino” of Messina were

included in the study. Each subject received a careful medical evaluation, including recording of past personal and family medical history, and physical examination. PHPT was diagnosed by the currently accepted laboratory and instrumental criteria (13). Fifty patients (40 F and 10 M, ratio F/M 4:1; median age 59.6 ± 16.6 years, range 37-82) underwent parathyroidectomy (PTx). The remaining 13 patients (9 F and 4 M, ratio F/M 2.5:1, median age 76.5 ± 6.2 years, range 64-83), who were ineligible for on unwilling to undergo surgery, were treated with cinacalcet. The 13 patients were candidate to medical treatment because they had a serum calcium concentration >1 mg/dL upper limit of normal. Patients initially received cinacalcet 30 mg twice daily. The dosage was increased to the next sequential dosage every 2 weeks, depending on the patient's serum calcium concentration during the previous week and an adverse event assessment. Dosage escalation continued until the serum calcium concentration was 10 mg/dl or less (2.5 mmol/liter). The observational period was 12 months from enrollment.

Informed consent was obtained, and the study was approved by our local Ethics Committee.

Methods.

Peripheral blood samples were collected after overnight fasting from all the recruited patients at baseline and at each follow-up visit. In the subset of patients under medical treatment, samples for serum calcium and PTH were collected before the morning dose of cinacalcet. Venous blood was centrifuged at $1450 \times g$ at 4°C for 10 min. Urine was collected over 24 h after an overnight fasting at baseline. All samples were processed centrally in the laboratory of our University Hospital of Messina. Serum calcium (normal values 8.4-10.4 mg/dl) and phosphorus (normal values 2.5-4.5 mg/dl), as well as urinary calcium and phosphorus (normal values 100-300 mg/24h and 300-800 mg/24h, respectively) and alkaline phosphatase (normal values 40-150), were measured using commercial kits on routine methods. Serum intact PTH was measured using a solid-phase, two-site, chemiluminescent, enzyme-labeled, immunometric assay (Immulite 2000; normal values 12–62 pg/ml in our laboratory). To evaluate the vitamin D status, 25(OH)D₃ was measured by HPLC (Bio-Rad Laboratories S.r.l., Milano, Italy). For all assays, the intra or the inter-assay CV were <5 and $<10\%$, respectively.

Statistical analysis

Data re expressed as mean \pm SD, median and range. Statistical analyses were performed by t test, using SPSS 17.0 for Window package. $P < 0.050$ two sided was considered to be statistically significant.

Results

Demographic, clinical and biochemical features of our study population are summarized in Table 1. Patients were divided in two groups: group A included 50 patients who underwent parathyroidectomy, group B included 13 patients who were treated with cinacalcet. As reported in Table 1, female sex was more represented in both groups (49 females, 14 males,

F:M ratio 3.5:1), and the median age at diagnosis was significantly higher in group B compared to group A patients (P=0.001). The two groups did not differ with respect to the main biochemical parameters at pre-surgical evaluation.

Table 1. Demographic, clinical and biochemical features of our study population

CINACALCET	PARATHYROIDECTOMY	P
No. of patients	13	50
Sex		
Male	4	10
Female	9	40
Age		
median \pm SD	76.5 \pm 6.2 (64-83)	59.6 \pm 11.3 (32-80)
Creatinine(mg/dl)	0.85 \pm 0.12 (0.6-1)	0.79 \pm 0.18 (0.6-1.3)
Urea (mg/dl)	39.6 \pm 5.7 (34-48)	37.9 \pm 6.5 (27-48)
Calcium(mg/dl)	11.7 \pm 0.4 (11.5-12.1)	11.5 \pm 1 (11.4-15)
Phosphorus(mg/dl)	2.9 \pm 0.3 (2.4-3.5)	3.0 \pm 0.4 (2.5-3.5)
Urinary calcium(mg/24h)	343.9 \pm 102.7 (37.5-476)	303.3 \pm 110.7(55.4-410)
Urinary Phosphorus(mg/24h)	497 \pm 95 (395-600)	470 \pm 89 (390-530)
25(OH)D₃(ng/ml)	29.8 \pm 10.5 (10.4-44)	29.88 \pm 8.7 (13-41)
PTH (pg/ml)	314.8 \pm 306.8 (65.7-869)	242.6 \pm 193.4 (65-1060)
Alkaline phosphatase (UI/L)	76 \pm 17.3 (66-96)	116.6 \pm 48.6 (55-201)

Indication for cinacalcet treatment were as follows: a) contraindication to PTx (n=10, 77%); b) PTx refusal (n=2; 15%); c) persistent PHPT after parathyroidectomy (n=1; 8%).

Group A

All patient who underwent PTx had a significant decrease in serum calcium 24 hours after surgery. Transient hypocalcemia occurred in 5 patients, requiring calcium supplementation for 2-4 weeks. In all patients serum calcium significantly decreased, reaching normal values at first evaluation 1 month after surgery (P=0.001) and at prolonged follow-up (P=0.001) (Table 2 and Fig. 1 A).

Intra-operative assessment of PTH was performed in 9 patients and showed a decrease of PTH by 74.7% compared to baseline in all but one patients (Table 3). In all patients PTH values decrease to normal values 24 hours after surgery and so remained during the whole duration of follow-up (P = 0.001 compared to baseline) (Table 2 and Fig. 1 A).

None had persistence or recurrence of PHPT.

Table 2. Calcium and PTH values during the follow-up

	Pre-surgery	Post-surgery			
		1° Month	3° Month	6° Month	12° Month
Group A					
Calcium (mg/dl)	11.5 ± 1 (11.4-15)	9.05 ± 0.85** (7-10.3)	9,3 ± 0,9** (4,4-10,6)	9,3 ± 0,5** (8,4-9,6)	9,2 ± 0,5** (8,2-9,7-9)
PTH (pg/ml)	242,6 ± 193,4 (65-1060)	68.6 ± 12.2** (3.3-75)	42,7 ± 17,9 ** (11,5-69,3)	57,1 ± 26,3** (13,5-72)	36,3 ± 6 *** (23,2-41)
	Pre-treatment	Post-treatment			
		1° Month	3° Month	6° Month	12° Month
Group B					
Calcium (mg/dl)	11.7 ± 0.4 (11.5-12.1)	10.5 ± 0.9* (9.6-12.3)	9.6 ± 0.7 ** (9.0-11.2)	9.5 ± 0.3 ** (9.1-9.9)	9.9 ± 0.3** (9.4-10.2)
PTH (pg/ml)	242,6 ± 193,4 (65-1060)	68.6 ± 12.2** (3.3-75)	42,7 ± 17,9 ** (11,5-69,3)	57,1 ± 26,3** (13,5-72)	36,3 ± 6 *** (23,2-41)

Group A: 50 patients undergone surgery. Group B: 13 patients under cinacalcet treatment. Data are mean + standard deviation.

*P=0.01; ** P=0.001; ***P=0.0001 compared to baseline

At pathological examination all but one patients were diagnosed with a benign parathyroid adenoma. One patient, an 80-year-old male, was found to have a parathyroid carcinoma, without any pre-operative suspicious of malignancy. Pre-operatively, he had elevated serum PTH (219.04 pg/ml; nv 12–62) and total (13.10 mg/dl; nv 8.2–10.4) and ionized calcemia (1.6 mmol/L; n.v. 1.1-1.3), as well as hypercalciuria (*410 mg/24hvitamina). Thus, this patient was not characterized by very high levels of serum calcium and PTH, as commonly expect in parathyroid cancer patients, and the diagnosis was made after surgery. As regards surgical complication, two patients experienced a transient dysphonia.

Group B

Of the 13 patients treated with cinacalcet, 9 completed the 12-month follow-up period, while 4 patients discontinued the treatment for adverse effects, 3 within the first month of therapy and one after 3 months. The most frequent adverse effects recorded were nausea resistant to therapy (50%), xerostomy (25%) and muscle spasms (25%). Nohypocalcemic events were recorded.

Cinacalcet was started at the dose of 30 mg twice daily and was increase to 60 mg twice daily in 6 patients within 4 weeks, until normal serum calcium was reached.

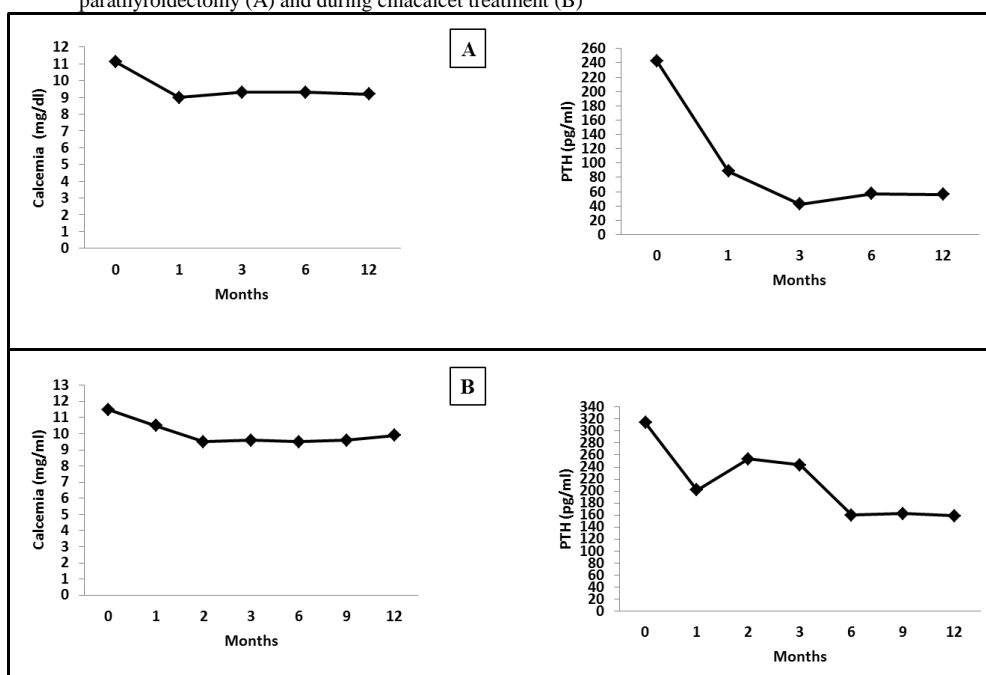
Serum calcium significantly decreased during titration phase of therapy (first month), despite it

was significantly higher compared to patients undergone PTx (10.5 ± 0.9 mg / dl vs 9.05 ± 0.85 mg/dl $P < 0.01$). Starting from month 2, all patient reached the maintenance cinacalcet dose (mean 30 mg twice daily, range 30 daily-60 mg twice daily), that remained constant during the following months. Starting from month 2, all patients achieved normal calcium values (≤ 10.2 mg/dl; 2.575 mmol/l). At last control (12 months), serum calcium was significantly reduced compared to baseline ($P = 0.01$) (**Table 2 and Fig. 1 B**) and was not different from the calcium values recorded in patients who had undergone PTx (9.9 ± 0.3 mg/dl vs 9.2 ± 0.9 mg/dl; $P > 0.05$). In all 13 patients PTH slightly decreased during follow-up (**Table 2 and Fig. 1 B**) and never reached a normal value.

Table 3. Intra-operative assessment of PTH

Pre-operative PTH	Intra-operative PTH	Reduction(%)
339 pg/dl	39 pg/dl	88,50
1060 pg/dl	279 pg/dl	73,68
263 pg/dl	42 pg/dl	84,0
218 pg/dl	83 pg/dl	61,93
131 pg/dl	90 pg/dl	31,30
131 pg/dl	26 pg/dl	80,15
120 pg/dl	28 pg/dl	76,67
3030 pg/dl	650 pg/dl	78,55
277 pg/dl	20 pg/dl	92,78

Figure 1. Changes in serum calcium and intact PTH from baseline over time after parathyroidectomy (A) and during cinacalcet treatment (B)



Discussion

In this study on a small cohort of patients suffering from PHPT, all subjects who received cinacalcet had their serum calcium lowered into the normal reference range during prolonged follow-up (12 months), as well as subjects who had undergone surgery. Serum PTH was lowered but did not normalize. Few non severe adverse effects (mainly, nausea) occurred and resolved following withdrawal from therapy. Thus, cinacalcet was proven to be effective in reducing and normalizing serum calcium in PHPT patients and was safe and well tolerated. However, serum PTH remained higher than normal range, suggesting limited beneficial effects of cinacalcet on the clinical manifestations of PHPT other than hypercalcemia (14). The effects of cinacalcet on skeletal manifestations of hyperPTH have not been evaluated in this study. However, evidence from the literature suggests no significant effects of cinacalcet on bone mineral density and/or fracture risk. Concomitant treatment with anti-catabolic drugs should be considered in PHPT patients with hypercalcemia and overt bone disease (14,15). Moreover, even though cinacalcet is effective in controlling hypercalcemia and well tolerated by most patients, the high costs could limit its use in the long-term management of PHPT patients.

In our experience, surgery has proved to be safe, with few transient complications, and effective, since none experienced disease persistence and/or recurrence. In our series, all patients achieved normal calcium and PTH levels 24 hour after operation, and the values remained within normal limits during the whole duration of follow up. One patient who underwent surgery was found to have a parathyroid cancer at histological examination, without pathognomonic symptoms and signs that could have raised pre-surgical suspicious. Despite accounting for approximately 1% of PHPT, parathyroid cancer is often difficult to diagnose pre-operatively and should be considered in the differential diagnosis, when choosing the treatment strategy of PHPT (16,17).

In line with results from previous studies (1), our results confirm that parathyroidectomy remains the first line curative approach to the majority of PHPT cases, while medical treatment with cinacalcet represents an effective alternative aiming reducing serum calcium in selected patients with PHPT (18-21). In 2008 the European Medicine Agency (EMA) has approved the use of cinacalcet to reduce hypercalcemia in patients with PHPT in whom parathyroidectomy is not clinically appropriate or is contraindicated, despite indicate on the basis of serum calcium levels (www.ema.europa.eu). More recently, cinacalcet has also been approved by the Food and Drug Administration (FDA) for treatment of severe hypercalcemia in patients with PHPT who are unable to undergo surgery (www.fda.gov). Patients with persisting PHPT after failed surgery or inoperable ones due to co-morbidities should also be offered medical therapy (22).

Finally, cinacalcet may be used to reduce calcium levels in preparation for parathyroidectomy (22).

The main limitation of the present study is the lack of any data concerning bone involvement in iperPTH patients and changes in bone density and fracture risk in the two groups of patients, the ones undergone surgery and those under medical therapy, during follow-up. A longer study evaluating also bone mineral density and fracture would be of value in assessing the long-term effects of cinacalcet.

In conclusion, surgery remain the mainstay in PHPT treatment, but cinacalcet treatment has gained prominence as a non-invasive treatment in selected PHTH patients, demonstrating to be effective in short- and long-term controls of hypercalcemia, though bone mineral density does not improve. More study and prolonged follow-up are necessary to better define the long term effects of cinacalcet on mortality and morbidity in PHTH and its safety.

Conflicts of interest: The authors declare no conflict of interest. Moreover, they have acquired the opinion of the Ethics Committee of Departement Veterinary Science (*Register number 033/19*).

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