Outcomes in patients with renal hyperparathyroidism requiring cinacalcet pre-operatively followed by parathyroidectomy

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ABSTRACT

Background: Cinacalcet is an effective treatment for renal hyperthyroidism when traditional medical therapy has failed. We studied the impact of pre-operative cinacalcet administration on post-surgical outcomes.

Methods: A retrospective analysis was performed of patients from 2002 to 2017 diagnosed with renal hyperparathyroidism requiring parathyroidectomy to evaluate the need for post-operative supplementation and outcomes.

Results: 102 patients were identified; 34 patients were treated with cinacalcet prior to undergoing parathyroidectomy. The cinacalcet treatment cohort (CT) demonstrated a greater duration of renal replacement therapy (p = 0.03) relative to the untreated cohort (NC). NC had greater proportion receiving peritoneal dialysis (p=<0.0001) compared to other forms of renal replacement, greater pre-operative PTH levels (p = 0.001) and greater decrease in PTH after resection (p = 0.0086). Post-operative vitamin D supplementation was more frequent in the CT group (p = 0.02). After propensity matching for pre-operative PTH and duration of renal replacement therapy, there were no differences in post-operative supplementation or outcomes.

Conclusions: Cinacalcet patients may have advanced disease. These patients have longer duration of renal failure and higher PTH levels. After propensity matching, no significant differences were noted in terms of need for supplementation or outcomes.

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Introduction

Secondary and tertiary renal hyperparathyroidism have complex pathophysiology in which chronic renal failure leads to parathyroid hyperplasia with decreased expression of vitamin D- and calcium-sensing receptors on the parathyroid cells and persistently elevated parathyroid hormone (PTH) production.[1,2] The resultant skeletal fractures, left ventricular hypertrophy, renal osteodystrophy and calciphylaxis (the deposition of calcium throughout the body) contribute to the long term morbidity and mortality of the disease.[3] Medical management of renal hyperparathyroidism with diet and dialysis modifications, supplementation with active vitamin D analogues and phosphate binders is unsuccessful in over a third of patients with renal hyperparathyroidism.[4] Historically, surgical intervention was indicated in patients who failed traditional medical therapy. Cinacalcet (Sensipar, Mimpara; Amgen), a calcimimetic agent, has been shown to be an effective medical alternative.[3] By allosteric binding of the calcium-sensing receptor, cinacalcet increases the sensitivity of parathyroid cells to extracellular ionized calcium,[3,5] decreasing PTH production with reduction in serum calcium and phosphate.[6]

Although calcimimetic agents have greatly improved the medical management of patients with renal hyperparathyroidism, there exists a subgroup of patients who fail this intervention and require surgery as definitive treatment. Surgery involves a subtotal parathyroidectomy with cervical remnant or a total parathyroidectomy with autotransplantation. Both procedures are well tolerated and have been demonstrated to reduce the long-term morbidity and mortality associated with renal hyperparathyroidism.[7,8]

Transient hypocalcemia following parathyroidectomy occurs in 30—90% of patients with renal hyperparathyroidism.[9,10] Mild

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reductions in serum calcium may lead to symptoms of muscle spasms and paraesthesias.[11] If left untreated, hypocalcemia can result in severe neurologic disability. To mitigate the potentially profound physiologic effects of post-operative hypocalcemia, these patients often require post-operative IV or oral calcium and vitamin D supplementation.

To date, there is scant information in the literature regarding surgical outcomes in patients who require surgery despite treatment with cinacalcet. The objective of this study was to characterize the post-operative requirements for calcium and vitamin D supplementation, hospital and intensive care length of stay, and 30-day readmission in patients at our institution who received cinacalcet treatment prior to parathyroidectomy, compared to those that did not receive cinacalcet treatment.

Methods

After obtaining approval from our institutional review board, a retrospective review was conducted of all patients who underwent parathyroidectomy at our institution from April 2002 through October 2017. Patients who underwent parathyroidectomy for primary hyperparathyroidism were excluded. Those patients with renal hyperparathyroidism secondary and tertiary were divided into two cohorts, a group that received cinacalcet prior to parathyroidectomy (CT) and a group that did not (NC).

The following data was collected for all patients by review of electronic medical records: general demographics including age and sex, duration of renal failure and dialysis including modality, type of renal hyperparathyroidism, dose and duration of time on cinacalcet treatment, pre- and post-operative serum calcium, phosphate, alkaline phosphatase and PTH levels, type of resection performed (total versus subtotal), post-operative calcium and vitamin D supplementation, hospital and intensive care length of stay and 30-day readmissions.

Continuous variables were reported as mean ± standard deviation for those with normal distributions, median with interquartile ranges for data with non-normal distributions, and percentages for proportions. The two groups were compared both in total and after propensity score matching to account for the greater pre-operative PTH level and duration of renal replacement therapy noted in the cinacalcet treated group. The groups were compared using Fisher exact test, student t-test and paired *t*-test as appropriate. Linear regression was used to correlate pre-operative PTH level and cinacalcet dose. A p-value of ≤0.05 was considered significant for all statistical analysis. Statistical analysis was performed using R statistical software and GraphPad Prism 7.

Results

Patient selection and demographics

Between April 2002 and October 2017, a total of 102 parathyroidectomies were performed on patients with renal hyperparathyroidism. At the attending surgeons' discretion, either a subtotal parathyroidectomy (3½ gland excision) or total parathyroidectomy with autotransplantation into the forearm was performed. Cervical thymectomy was not routinely performed. Of these 102 parathyroidectomies, 34 were performed on patients treated pre-operatively with cinacalcet, while 68 were performed on patients not treated with cinacalcet. One patient underwent a repeat procedure at our institution leaving a total of 33 unique patients for analysis in the CT cohort. The CT cohort included 5 other patients who were undergoing repeat procedures with the original operation performed at outside institutions, while the NC cohort had 6 patients undergoing repeat procedures. Patient

demographics, extent of renal disease and operative types in each group along with cinacalcet dosages are given in Table 1. Comparison of the CT and NC groups demonstrated significantly increased duration or renal replacement therapy (median (25th,75th percentile) for CT: 4 years (2, 8); NC: 2 years (1, 5); p = 0.03) and larger tendency for peritoneal dialysis as the modality of renal replacement (22% vs 9%; p=<0.0001) in the NC group. The NC group patients more frequently underwent a total parathyroidectomy with autotransplantation (43% versus 15%; p = 0.007). Linear regression of our data demonstrated minimal correlation between pre-operative PTH levels and cinacalcet dose (R = 0.245).

Pre & post-operative laboratory values

Table 2 displays the pre-operative lab values for the NC and CT groups respectively, along with changes after parathyroidectomy. Both the CT and NC groups had significant changes in calcium, calcium phosphate product and parathyroid hormone, while the CT group also demonstrated a significant change in phosphate levels. Comparison of the CT and NC groups demonstrated similar laboratory changes with the exception of significantly elevated parathyroid hormone levels in the CT group, including both pre-operative PTH (CT: Median (25th,75th percentile) of 1385 (987, 2072); NC: 580 (303, 1435); p = 0.001) and decease in PTH after parathyroidectomy (CT: −1277 (−1775, −835) NC: −593 (−1379, −270); p = 0.0086).

Post-operative calcium & vitamin D supplementation

Post-operative oral calcium and vitamin D (calcitriol) supplementation was administered at the discretion of the attending surgeon. The indication for supplementation by intravenous calcium was symptomatic hypocalcemia (paraesthesias, muscle spasms). Patients in the CT group received supplemental vitamin D (calcitriol) more frequently than in the NC group (79% vs. 52%, p = 0.02). In our study cohort, 42% of CT patients required intravenous calcium supplementation for symptomatic hypocalcemia, compared to 25% of NC patients (p = 0.07). Oral calcium supplementation tended to be more frequent in the cinacalcet treated cohort (91% vs. 77%) but did not achieve significance (p = 0.10) (Table 2).

Hospital & ICU length of stay, readmission rates

The CT group had a tendency for longer hospital length of stay (CT: Median (25th;75th percentile) of 4 days (2, 6); NC: 2 days (1, 5); p = 0.72) and surgical intensive care unit length of stay among those that required ICU care (CT: 4 days (3, 7); NC: 2.5 days (2, 13); p = 0.66); however, these differences did not achieve significance. The overall rate of intensive care unit admission (CT: 15%, NC: 15%; p = 1) as well as the 30 day readmission rate (CT: 6%, NC: 10.8%; p = 0.71) were not different between the groups (Table 2). Regarding SICU admission, half were due to hypocalcemia and the other 50% for other indications including post-operative MI (1), prior admission to ICU (2), caliphlaxis related prolonged intubation after surgery (1) and airway monitoring for a neck hematoma (1). In contrast, all SICU admissions in the cinacalcet treated group were related to hypocalcemia.

Propensity score matching analysis

In an attempt to isolate the effect of cinacalcet on outcomes, propensity score matched analysis was performed. The 33 patients in the CT group were propensity matched to 33 patients in the NC

Table 1
Patient demographics, complete cohort.

	No Cinacalcet (N = 68)	Cinacalcet (N = 33)	P-Value
Age (years)	49.7 ± 15.1	45.1 ± 13.8	0.14
Gender (% male)	51.4% (35)	57.6% (19)	0.67
Duration of Renal Failure (years)	6 (4, 11)	7 (5, 11)	0.15
Duration on Dialysis	2 (1, 5)	4 (2, 8)	**0.03**
Type of Renal Replacement			
Hemodialysis	57% (39)	76% (25)	0.08
Peritoneal Dialysis	22% (15)	9% (3)	**<0.0001**
Status Post Renal Transplant	6% (4)	6% (2)	1
None	15% (10)	9% (3)	0.54
Type of Hyperparathyroidism			1
Secondary	76% (52)	79% (26)	
Tertiary	24% (16)	21% (7)	
Type of Surgery			**0.02**
Subtotal Parathyroidectomy	49% (33)	70% (23)	0.06
Total with Autotransplantation	43% (29)	15% (5)	**0.007**
Repeat Operation	9% (6)	15% (5)	0.33
Cinacalcet Duration of Treatment (years)	0	1 (1, 2)	
Cinacalcet Dose (mg)	0	60 (30,90)	

Values are reported as mean ± standard deviation or median with interquartile range (25th, 75th). Percentage values include (number of patients).

groups based on age, sex, and the two pre-operative variables that were most significantly different between the groups, duration of renal replacement therapy and pre-operative PTH levels. After matching, the analysis failed to demonstrate any differences in baseline demographics (Table 3), or laboratory values (Table 4) with the exception of modestly but significantly lower levels of both pre and post-operative alkaline phosphatase levels in the CT group (p = 0.02, p = 0.04, respectively) and overall decrease in serum

Table 2
Laboratory analysis and post-operative outcomes, complete cohort.

	No Cinacalcet (N = 68)[a]	Cinacalcet (N = 34)[b]	P-value for comparison between groups
Calcium			
Pre-operative	9.9 ± 1.1	9.5 ± 1.2	0.08
Post-operative	8.2 ± 1.1	8.1 ± 1.2	0.72
Change	−1.6 ± 1.4	−1.4 ± 1.3	0.49
	p < **0.0001**	p < **0.0001**	
Phosphate			
Pre-operative	5.0 ± 2.3	5.7 ± 2.3	0.15
Post-operative	4.7 ± 1.7	5.1 ± 2.0	0.37
Change	−0.25 ± 1.8	−0.44 ± 1.7	0.61
	p = 0.28	p = **0.03**	
Calcium Phosphate Product			
Pre-operative	46.6 ± 24.3	50.5 ± 24	0.45
Post-operative	36.5 ± 14.4	39.4 ± 16.9	0.37
Change	−8.4 ± 18.6	−11 ± 15.3	0.48
	p < **0.0001**	p < **0.0001**	
Alkaline Phosphatase			
Pre-operative	128.5 (85, 202)	182 (133, 252)	0.24
Post-operative	130 (93, 273)	189 (134, 286)	0.52
Change	12 (−16, 52)	17 (−11, 54)	0.84
	p = 0.24	p = 0.58	
Parathyroid Hormone (pg/dL)			
Pre-operative	580 (303, 1435)	1385 (987, 2072)	**0.001**
Post-operative	42 (8, 110)	84 (23, 199)	0.055
Change in PTH	−593 (−1379, −270)	−1277 (−1775, −835)	**0.0086**
	p < **0.0001**	p < **0.0001**	
% Decrease	94% (85, 99)	92% (88, 97)	0.43
% Below 250 pg	91% (52)	76% (25)	0.06
% Below 65 pg	60% (34)	42% (14)	0.13
IV Calcium supplementation	25% (17)	42% (14)	0.07
PO Calcium supplementation	77% (52)	91% (30)	0.10
Dose, mg elemental calcium/day	720 (330, 1520)	1200 (600, 1600)	0.10
Vitamin D (calcitriol) supplementation	52% (35)	79% (26)	**0.02**
Dose, IU/day	0.25 (0, 0.5)	0.5 (0.25, 0.5)	0.38
Hospital Length of Stay	2 (1, 5)	4 (2, 6)	0.72
SICU Admission	15% (10)	15% (5)	1
SICU Length of Stay	2.5 (2,13)	4 (3,7)	0.66
Readmission (30 Day)	10.8% (7)	6% (2)	0.71

Values are reported median with interquartile range (25th, 75th). Percentage values include (number of patients). IV = intravenous, PO = per os, oral administration, SICU = surgical intensive care unit.
  [a] Values from N = 68 surgeries except alkaline phosphatase, N = 64; Change in PTH, N = 57; postoperative outcomes, N = 67.
  [b] Values from N = 34 surgeries except PTH levels, N = 33; Phosphate, phosphate product and alkaline phosphatase, N = 32.

Table 3
Patient demographics, propensity matched cohorts.

	No Cinacalcet (N = 33)	Cinacalcet (N = 33)	P-Value
Age (years)	48.0 ± 16.6	45.1 ± 13.8	0.43
Gender (% male)	48.5% (16)	57.6% (19)	0.62
Duration of Renal Failure (years)	5 (4, 12)	7 (5, 11)	0.56
Duration on Dialysis	4 (3, 5)	4 (2, 8)	0.21
Type of Renal Replacement			
Hemodialysis	73% (24)	76% (25)	1
Peritoneal Dialysis	18% (6)	9% (3)	0.48
Status Post Renal Transplant	3% (1)	6% (2)	1
None	6% (2)	9% (3)	1
Type of Hyperparathyroidism			0.51
Secondary	88% (29)	79% (26)	
Tertiary	12% (4)	21% (7)	
Type of Surgery			
Subtotal Parathyroidectomy	70% (23)	70% (23)	1
Total with Autotransplantation	27% (9)	15% (5)	0.37
Repeat Operation	3% (1)	15% (5)	0.2
Cinacalcet Duration of Treatment (years)	0	1 (1, 2)	
Cinacalcet Dose (mg)	0	60 (30, 90)	

Values are reported as mean ± standard deviation or median with interquartile range (25th, 75th). Percentage values include (number of patients).

calcium levels after resection (p = 0.03). There were no significant differences in the need or decision to supplement calcium or vitamin D, or the post-operative outcomes of hospital or SICU length of stay or 30 day readmissions (Table 4).

Discussion

This study sought to evaluate the post-surgical outcomes after parathyroidectomy for renal hyperparathyroidism patients who were treated pre-operatively with the calcimemetic agent cinacalcet compared to those that were untreated, using a propensity score matched analysis in an attempt to correct for significant difference between the two cohorts, namely the significantly greater pre-operative PTH level and duration of renal replacement therapy seen in the cinacalcet treated cohort. To date, there is little data evaluating patients that have failed medical treatment with cinacalcet.

In our study cohort, 42% of CT patients required intravenous calcium supplementation for symptomatic hypocalcemia, compared to 25% of NC patients. Oral calcium supplementation

Table 4
Laboratory analysis and post-operative outcomes, propensity matched cohort.

	No Cinacalcet (N = 33)	Cinacalcet (N = 33)	P-value for comparison between groups
Calcium			
Pre-Operative	9.8 ± 0.8	9.5 ± 1.2	0.26
Post-Operative	7.8 ± 1.0	8.1 ± 1.2	0.20
Change	2.0 ± 0.9	−1.4 ± 1.3	**0.03**
Phosphate			
Pre-Operative	5.3 ± 1.9	5.7 ± 2.3	0.47
Post-Operative	5.0 ± 1.6	5.1 ± 2.0	0.79
Change	0.4 ± 1.6	−0.44 ± 1.7	0.86
Calcium Phosphate Product			
Pre-Operative	53.7 ± 20.9	50.5 ± 24	0.69
Post-Operative	40.7 ± 15.6	39.4 ± 16.9	0.49
Change	−12.6 ± 14.0	−11.0 ± 15.3	0.86
Alkaline Phosphatase			
Pre-Operative	241 (151, 534)	182 (133, 252)	**0.01**
Post-Operative	273 (166, 717)	189 (134, 286)	**0.02**
Change	14 (−51, 70)	21 (−60, 12)	0.88
Parathyroid Hormone			
Pre-Operative	1644 (7832, 3033)	1468 (964, 2189)	0.42
Post-Operative	66 (12, 205)	85 (22, 250)	0.35
Change	−1703 (766, 2753)	−1277 (832, 1856)	0.11
% Decrease	93% (88, 99)	92% (87, 97)	0.32
% Below 250	80% (24/30)	76% (24/30)	0.77
% Below 65	50% (15/30)	42% (14)	0.62
Intravenous calcium supplementation	52% (17)	42% (14)	0.62
PO calcium supplementation	88% (29)	94% (31)	0.67
Dose, mg elemental calcium/day	1800 (900, 3800)	1200 (600, 1600)	0.08
Vitamin D (calcitriol) supplementation	67% (22)	79% (26)	0.41
Dose, IU/day	0.5 (0, 0.75)	0.5 (0.25.0.5)	0.55
Hospital Length of Stay	5 (2, 6)	4 (2, 6)	0.59
SICU Admission	21% (7)	15% (5)	0.75
SICU Length of Stay	2 (2,2)	4 (3, 7)	0.84
Readmission (30 Day)	6% (2)	6% (2)	1

Values are reported as mean ± standard deviation or median with interquartile range (25th, 75th). Percentage values include (number of patients).
IV = intravenous, PO = per os, oral administration, SICU = surgical intensive care unit.

tended to be more frequent in the cinacalcet treated cohort (91% vs 77%) but did not achieve significance (p = 0.10). Vitamin D (calcitriol) supplementation was significantly more frequent in the cinacalcet treated cohort (p = 0.02). In a similar study of 110 patients on cinacalcet, Wirowski et al. found a nearly identical proportion of patients requiring oral calcium supplementation but a lower proportion receiving supplemental vitamin D.[7] It is likely that patients failing pre-operative treatment with cinacalcet were started on vitamin D and oral calcium immediately after surgery in anticipation of the transient hypocalcemia and hypophosphatemia that has been reported with cinacalcet use.[3] Of note, our institution does not have a formalized protocol, either biochemical or clinical, for post-operative calcium and vitamin D supplementation, with the decision to administer and the dosing at the discretion of the treating surgeon or endocrinologist.

Patients in our study achieved a median 92% reduction in PTH levels in the CT cohort and 94% in the NC cohort, which may have contributed to a relatively high rate of symptomatic hypocalcemia and requirement for calcium and vitamin D supplementation. However, intravenous calcium supplementation was almost exclusively reserved for cases of symptomatic hypocalcemia. In addition, a similar frequency in both cohorts required admission to an intensive care unit (15% in each). The median length of stay after parathyroidectomy was 4 days (2, 6) in the CT group and 2 (1, 5) in the NC group, which is lower than other studies citing length of stays of 5 and 5.5 days.[4,7]

Patients in our study had a median PTH level of 1385 pg/dL in the CT cohort and 580 in the NC cohort. Severe elevation of hormone levels may result from the longer duration and severity of the disease, with the greater post-operative decrease in PTH making these patients more susceptible to post-operative hypocalcemia. This may have clinical implication in patients with nodular hyperplasia, as these patients are more likely to be resistant to calcimimetic therapy. These patients have been demonstrated to have downregulation of the calcium sensing receptor CaSR on parathyroid cells and may benefit from earlier surgical intervention.[12–14] Prior studies have demonstrated pre-operative PTH levels are higher in patients treated with cinacalcet relative to patients with renal hyperaparathyroidism not on calcimimetic therapy.[15]

To account for the influence of disease duration and severity, a propensity matched analysis was performed between the two groups allowing 33 patients in the cinacalcet treated group to be matched to 33 patients in the untreated group based on age, sex, the pre-operative PTH level and the duration of renal replacement therapy. In these matched cohorts, there were no significant differences in Vitamin D or calcium supplementation between patients who received cinacalcet and those who did not. This suggests that the administration of cinacalcet pre-operatively does not independently put these patients at an increased risk for post-operative hypocalcemia and the need for supplementation. However, as both these groups of patients had higher pre-operative PTH levels and thus had greater decreases in PTH following surgery, they received careful post-operative monitoring for hypocalcemia, and in our study a higher percentage received supplementation than the group of all the NC patients.

It is important to note that an extremely elevated intact PTH level may influence a clinician to first, start a patient on cinacalcet and second, to use the degree of elevation in determining what dose to prescribe. However, linear regression of our data demonstrated minimal correlation between pre-operative PTH levels and cinacalcet dose (R = 0.245), suggesting PTH levels may not have had a significant influence on the cinacalcet dosing regimen chosen by study clinicians. This group of patients may have been selected for cinacalcet administration after resistance to treatment with conventional medications including phosphate binding medications and vitamin D analogues, or have a different physiology that made their PTH levels higher at baseline. This potentially advanced disease severity may have warranted broadening of the medical treatment options to include cinacalcet therapy. Whether higher baseline PTH levels were the result of advanced disease severity or if there was a selection bias is unclear, and the retrospective nature of this study makes it an inherent limitation.

The greatest limitation of this study is the lack of a protocol at our institution for the administration of post-operative calcium or vitamin D supplementation based on laboratory values or clinical evaluation. All intravenous calcium was administered to patients in this study only for symptomatic hypocalcemia. This makes utilizing the frequency and dose of supplementation as measures of disease severity of limited utility and results must be viewed with this caveat in mind.

Another limitation is the sample size of our study population. The small sample size of 102 parathyroidectomies for renal hyperparathyroidism with only 34 of those in cinacalcet treated patients provides limited power to adequately demonstrate statistically significant predictors of post-operative outcomes. Given that these patients were accrued over a period of 15 years at our institution, any study with the necessary sample size to achieve more robust power to detect these predictors would likely need to be a multi-institutional analysis.

Conclusion

In summary, renal hyperparathyroidism patients requiring surgery after treatment with cinacalcet may represent a patient population with advanced disease severity. Cinacalcet-treated patients more often required post-operative supplementation with calcium and vitamin D than those who had not been prescribed cinacalcet; however, after propensity matching for pre-operative parathyroid hormone level and duration of renal replacement therapy, these differences were not retained. This suggests that cinacalcet use itself is not an independent predictor of post-operative hypocalcemia. This information may be of value to clinicians in predicting the post-operative supplementation requirements in renal hyperparathyroidism patients with extremely elevated parathyroid hormone levels.

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