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THE EFFECT OF CHRONIC KIDNEY DISEASE ON INTRAOPERATIVE PARATHYROID HORMONE:

A LINEAR MIXED MODEL ANALYSIS

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Article Summary

Among patients undergoing parathyroidectomy for primary hyperparathyroidism, those with chronic kidney disease have significantly higher parathyroid hormone levels than those with normal renal function, but there is no difference in rate of decline over time. These findings indicate that the Miami criterion can be used with confidence in this patient population, but additional time points may be required for normalization of parathyroid hormone values.

Abstract

Background

Reduced creatinine clearance is an indication for surgery in asymptomatic primary hyperparathyroidism (PHPT), and a significant proportion of patients undergoing parathyroidectomy have chronic kidney disease (CKD). The purpose of this study was to evaluate the kinetics of intraoperative parathyroid hormone (IOPTH) decline during parathyroidectomy in patients with CKD compared to those with normal renal function (NRF).

Methods

This is a single center, retrospective study of patients with PHPT undergoing parathyroidectomy (n=646). Patients were grouped based on estimated Glomerular Filtration Rate (eGFR) greater than (NRF) or less than (CKD) 60 mL/min/1.73m^2. All patients had IOPTH monitoring and ≥ 6-month post-op serum studies to confirm surgical cure. IOPTH kinetic curves were analyzed using a linear mixed model.

Results

Despite similar pre-excision values, patients with CKD had significantly higher IOPTH values at 5 minutes (76 vs. 58 pg/mL, p=0.02) and 10 minutes (54 vs. 37 pg/mL, p=0.004) post-excision. There was no significant difference in whether patients met Miami criterion by 5 minutes (CKD 71%, NRF 78%, p= 0.255) or by 10 minutes (CKD 95%, NRF 96%, p=0.751) post-excision. Using a linear mixed model, GFR did not have a significant effect on the change in IOPTH over time.

Conclusions

Patients with CKD had significantly higher post-excision IOPTH levels. However, renal function did not affect the change in IOPTH over time, nor did renal function ultimately affect the likelihood of meeting the Miami criterion. IOPTH monitoring remains useful in this population, though additional time points may be needed to see normalization of values.

Background

Primary hyperparathyroidism (PHPT) is caused by the autonomous production of parathyroid hormone (PTH) by abnormal parathyroid glands. This overproduction results in metabolic derangements, usually with elevated calcium levels.[1] PHPT is caused by a solitary adenomatous gland in approximately 80% of cases and can present with a wide array of symptoms.[2] Surgical excision of diseased glands is the only cure and can provide improved long-term quality of life.[3]

The prevalence of renal insufficiency is approximately 13-35% in patients undergoing parathyroidectomy for hyperparathyroidism.[4] Creatinine clearance < 60 mL/min continues to be a recommended criterion for parathyroidectomy in the latest consensus guidelines.[5] Resolution of hyperparathyroidism by surgical resection has been shown to halt the progression of or improve renal insufficiency.[6,7]

Real-time intraoperative PTH (IOPTH) monitoring has been invaluable for assessing parathyroid function during minimally-invasive parathyroidectomy.[8,9] Numerous IOPTH criteria exist in the literature, and their use vary by institution. The revised Miami criterion is one such example and provides a guideline for intraoperative decision making. A drop in IOPTH after removal of suspicious glands ≥50% from the higher of either pre-incision or immediately pre-excision levels predicts normocalcemia at 6 months at the same rate as bilateral neck exploration.[10,11] The criterion has withstood the test of time, with accuracy ranging from 97 – 98% in predicting cure.[12]

PTH is metabolized largely by the liver and kidneys with some contribution from peripheral oxidation.[13] Differences in PTH clearance rate could have significant impacts on the applicability of IOPTH criteria. The impact of patient characteristics on IOPTH kinetics have yet to be completely elucidated. Clearer understanding is

important because intraoperative decisions can change based on IOPTH monitoring, which may lead to unnecessarily extended anesthetic exposure and surgical explorations.[14] Recent studies have investigated various factors that may alter PTH metabolism and thus the utility of IOPTH monitoring.[15–17]

The objective of this study was to evaluate the kinetics of IOPTH decline during parathyroidectomy in patients with renal insufficiency and to assess whether the Miami criterion can be appropriately applied to this patient population.

Methods

This study was a single-institution, retrospective case-control study of patients undergoing parathyroidectomy for PHPT from June, 2006 to October, 2014. This study was approved by our Institutional Review Board, Protocol AAAL3823. Demographic information, preoperative laboratory studies, IOPTH measurements, and postoperative laboratory data were collected retrospectively from the electronic medical record system. Patients were excluded if they underwent surgery for secondary or tertiary hyperparathyroidism, had prior parathyroid surgery, or if they had incomplete or missing data regarding preoperative and postoperative calcium or intact parathyroid hormone values. Patients were separated into normal renal function (NRF) and chronic kidney disease (CKD) groups based on estimated Glomerular Filtration Rate (GFR). Patients were considered to have CKD if their most recent preoperative GFR was < 60 mL/min/1.73m^2. Normal ranges of calcium and PTH from each patient's referring institution or laboratory were used to define their biochemical profile as typical (elevated calcium, elevated PTH), normocalcemic (normal calcium, elevated PTH, no evidence of secondary hyperparathyroidism), and normohormonal (elevated calcium, unsuppressed PTH) biochemical profiles.

Secondary causes of elevated PTH, including vitamin D deficiency, hypercalciuria, and medication-induced hyperparathyroidism were excluded in all patients prior to surgery, and all atypical biochemical profile patients were referred for multidisciplinary evaluation to Columbia University Medical Center's Metabolic Bone Diseases Unit for confirmation of their diagnosis prior to their operation.

It is our practice to request 6-month and 1-year postoperative calcium and intact parathyroid hormone laboratory values from patients' primary care physicians or endocrinologists, and these values were used to confirm biochemical cure after parathyroidectomy. A 6-month post-parathyroidectomy time course has been established as the standard period to determine cure as well as to distinguish between persistent and recurrent disease.[1] Patients with typical and normohormonal profiles were considered to be cured with normal serum calcium. Given that they had normal pre-operative calcium levels, patients with the normocalcemic variant were judged by stricter criteria and considered cured if they had a normal calcium and PTH level at least 6 months postoperatively.

All patients had intraoperative parathyroid hormone monitoring, which was performed using a standard institutional protocol: a baseline measurement was obtained after induction but before surgical incision from peripheral blood, typically via an angiocath in the antecubital fossa. Once the adenoma was identified and dissected, a pre-excision ("time 0") measurement was obtained just prior to ligation of the vascular pedicle. All patients then had at least two additional measurements: a five-minute post-excision measurement and a ten-minute post-excision measurement. If these levels did not drop below 50% of the higher of the first two levels (baseline or time 0), thereby meeting the Miami criterion, then additional levels were drawn as needed, and/or patients were re-explored at the surgeon's

discretion. IOPTH monitoring was performed using the STAT-IO-I-PTH Assay (Future Diagnostics, Netherlands), a 2-site chemiluminescent immunometric assay using two affinity purified goat polyclonal antibodies to detect intact PTH. Normalization of PTH was measured using our institution's upper limit of normal, <= 74 pg/mL. Intraoperative ultrasound after induction of anesthesia was not routinely performed in these patients.

Patient demographic and biochemical data were analyzed with the Mann-Whitney two-sample statistic, chi-square analysis, or Fisher's exact test. For analysis of IOPTH curves, only patients with confirmed biochemical cure were analyzed. IOPTH values were log-transformed prior to analysis to normalize their distribution. To account for patient-level variance, repeated IOPTH serum measurements were modeled using a linear mixed model with GFR as both a continuous and a binary variable (NRF vs CKD). To analyze whether GFR modified the change of IOPTH measurements over time, time was treated as a categorical variable and an interaction term between GFR and time was modeled. An additional model including age (continuous variable), sex, race/ethnicity, biochemical profile, and single vs. multi-gland disease (categorical variables) as covariates was also performed. Individual subjects were set as the random effects, covariates were set as the fixed effects parameters, and an unstructured covariance-variance matrix was used. Significance was set at $P < 0.05$. Statistical analyses were performed with SAS (SAS, Cary, NC) and STATA (Stata-Corp, College Station, TX) software.

Results

From April 2006 to October 2014, 821 patients who underwent parathyroidectomy for hyperparathyroidism were identified. Patients were excluded

if they carried a diagnosis other than PHPT, had previous parathyroid surgery, or were missing significant pre- or intra-operative data, such as GFR or IOPTH values (114 patients). An additional 61 patients were excluded for lack of at least 6-month follow-up data, leaving 646 patients for analysis. Median follow-up was 12 months (range 6–62).

Demographic, pre-operative, and intra-operative characteristics of this cohort are described in Table 1. Of the 646 patients, 590 (91%) had NRF, while 56 (9%) had CKD. Patients with CKD were significantly older and more likely to have multi-gland disease. There was no difference between groups in biochemical cure at least 6 months after surgery (CKD 95% vs. NRF 97%, p=0.223). Among patients with biochemical evidence of cure at least 6 months post-operatively (n=627; CKD=53, NRF=574), there was no difference in the baseline or pre-excision (“time 0”) IOPTH values between patients with NRF and CKD. However, patients with CKD had significantly higher IOPTH values than patients with NRF at 5 minutes and 10 minutes post-excision (Table 2). Figure 1 demonstrates the IOPTH decline from highest pre-excision value to 5- and 10-minutes post-excision.

There was no significant difference in whether patients met Miami criterion by 5 minutes (CKD 71%, NRF 78%, p= 0.255) or by 10 minutes (CKD 95%, NRF 96%,p=0.751) post-excision. Patients with CKD were less likely to have IOPTH fall into the normal range by 5 minutes post-excision (CKD 47%, NRF 62%, p=0.038). By 10 minutes, patients with CKD remained less likely to normalize, but the difference was no longer significant (CKD 73%, NRF 80%, p=0.268). There was no significant difference in whether patients met “dual criteria” (>50% decrease from the pre-incision level plus PTH into the normal range) by 10 minutes (CKD 73%, NRF 77%, p=0.507).

In a linear mixed model (Table 3) of predictive variables of IOPTH measurements (GFR as a continuous variable and time as a categorical variable), both GFR and time are significant predictors of IOPTH. However, the interaction between GFR and time, modeling the effect of GFR on the change in IOPTH over time, was not significant. With GFR as a categorical variable (NRF vs. CKD), again, GFR and time are significant predictors of IOPTH, but GFR was not a significant predictor of change in IOPTH over time (Table 4).

Akaike's information criterion was used to determine that GFR as a categorical variable, as opposed to a continuous variable, was a more appropriate fit for a multivariable linear mixed model. Therefore, our multivariable model (Table 5) included GFR as a categorical predictive variable of IOPTH measurements, along with age, sex, race/ethnicity, biochemical profile, and multi-gland disease as covariates. In this model, age and biochemical profile were both independent significant predictors of IOPTH, along with GFR and time. However, again, the GFR and time interaction was not a significant predictor of IOPTH change over time. The model's predicted IOPTH curves for patients with CKD and NRF are shown in Figure 2.

Discussion

The main purpose of this study was to evaluate the kinetics of IOPTH decline during parathyroidectomy in patients with CKD compared to NRF, and to demonstrate the applicability of the Miami criterion in these patients. Previous studies have indicated that the rate of PTH decline in patients with renal impairment is slower;[16] however, the rate of meeting cure criteria is not affected.[18] Other studies have shown that renal function does not have a significant effect on intraoperative

PTH kinetics.[15,19] Egan *et al.* demonstrated higher PTH levels at all post-excision timepoints, but validated the use of the Miami criteria in predicting cure for patients with CKD stages II-III and recommended additional measurements at 20 minutes post-excision for select patients with CKD stages IV-V for reassurance of adequate resection.[20] The Miami group showed that long-term normocalcemia after several months was not significantly different between patients with stage I-II and stage III renal insufficiency when the 50% drop from pre-excision value criteria was used.[4] This same group has suggested, however, that long-term cure rates can be increased by including a drop to normal parathyroid hormone to their criteria.[21]

Review of our institutional data showed that, given similar baseline and pre-excision PTH levels, patients with renal insufficiency had higher IOPTH values at both post-excision timepoints. The univariable linear mixed models indicated that lower GFR was associated with higher IOPTH values, when GFR was used as both a continuous and a categorical variable. Neither univariable model showed a significant effect of GFR on the change of IOPTH over time. In our multivariable linear mixed model, reduced renal insufficiency was again significantly associated with higher IOPTH levels. The GFR*time interaction, which modeled GFR's effect on IOPTH over time, again was not significant. Thus, while post-excision IOPTH values are higher in patients with reduced renal function, the degradation kinetics are not significantly different.

We did not find a difference in achieving the Miami criterion between patients with NRF and CKD. In our study, only 19 patients overall were not cured, of which 16 had NRF and 3 had CKD. Unfortunately, these small numbers do not allow for the necessary power to determine the predictive value of the Miami criterion for long-term biochemical cure. In a similar investigation on IOPTH kinetics, Sohn *et al*.

separated patients into CKD and NRF groups and fitted IOPTH data via linear regression to determine slope of fit lines.[18] Their study determined that the percentage declines from baseline at 5-, 10-, and 15-minutes were significantly different, and that the slopes from 0 – 10 minutes were not significantly different, which we corroborate with our data. We elected to use a linear mixed model in our study to account for repeated measures among patients, as well as patient-level variance; IOPTH measurements are correlated within each patient, rather than being treated as independent observations.

Our multivariable linear mixed model identified age and biochemical profile as having independently significant effects on IOPTH in addition to GFR and time. According to our model, a one-year increase in patient age will increase a measured IOPTH level by 1.005 pg/mL. Advanced age has previously been shown to be an independent predictor of slower IOPTH decline.[16] However, the true effect of age on the applicability of the Miami criterion may be difficult to ascertain as different age groups may have disparate comorbidities and biological profiles. For instance, Leiker *et al.* showed that age alone was not predictor of IOPTH kinetics, but did interact with BMI in determining its effect on PTH half-life.[15] In Shawky *et al.*'s large retrospective study evaluating common clinical variables and their effects on IOPTH kinetics, age was associated with greater IOPTH at all points, but it did not affect long-term cure when using the Miami criterion.[22] Indeed, the Miami criterion has been shown to mitigate the age-related challenges of preoperative diagnosis uncertainty with comparable cure rates between the extremes of age groups.[23]

Biochemical profile also had an independently significant effect on IOPTH in our analysis. PHPT has classically been diagnosed with the concurrent elevations of PTH and calcium. However, two additional variants of PHPT are now recognized:

normocalcemic (NC) and normohormonal (NH).[24] NC HPT is characterized by normal calcium and elevated PTH without secondary causes of PTH elevation. NH HPT is characterized by elevated calcium with a paradoxically normal or unsuppressed PTH. Our previous work investigated the effect of biochemical profile on IOPTH and demonstrated a slower rate of IOPTH decline in NC[25,26] and NH[27] patients compared to typical profile patients. Surgical resection of adenomatous glands have been shown to be beneficial in both NC[28–30] and NH[31] groups. In detailed analyses of long-term cure with respect to IOPTH criteria, Trinh *et al.* demonstrated comparable outcomes for NC patients as long as a >50% IOPTH drop was achieved.[26] Furthermore, NH patients had worse outcomes when the >50% IOPTH drops were reached at ≥10 post-excision time points.[27]

Patients with both single-gland (n = 552) and multi-gland (n = 94) disease were included in our model, and patients in the CKD group had proportionally higher rates of multi-gland disease. This theoretically increases the risk that, particularly in patients with 4-gland hyperplasia, some abnormal tissue remained in situ during IOPTH measurements. However, there was no difference in biochemical cure rates between groups. An additional linear mixed model including patients with only single-gland disease showed a similar pattern as the all-inclusive group (supplementary data).

All IOPTH measurements were obtained from the STAT-IO-I-PTH® Assay, a 2-site “second-generation” chemiluminescent immunometric assay. Though second-generation assays were designed to measure only full-length intact PTH, studies have demonstrated that these assays also measure some non-intact 7-84 PTH fragments, particularly in uremic patients.[32] New third-generation assays, which only measure whole 1-84 PTH, are now known to be the most accurate method of

measuring PTH.[33] Measurement of IOPTH with a third generation assay has shown more rapid decrease than that measured with a second-generation assay.[34] Moreover, recent data also suggests an effect of GFR on rate of decrease in IOPTH with a second-generation assay, while there was no difference using a third-generation assay.[35] Without the direct comparison of measurements with a third-generation assay, the extent to which our use of a second-generation assay may have affected IOPTH kinetics is unknown. We hope to continue our study of this fascinating topic by conducting a similar analysis using a third-generation assay.

This study design has limitations due to its retrospective and observational nature. Although complete for most of the data points collected, there were some missing variables, and some continuous variables had minimum or maximum value cutoffs that may have affected analyses. Our database did not include information on prior cervical surgery other than parathyroidectomy, which may have led to previous parathyroid injury or devascularization. We were also unable to incorporate data on preoperative planning and intraoperative decision-making, and thus are unable to determine whether operative plan changed based on IOPTH. To minimize selection bias, we attempted to include all patients with a preoperative diagnosis of PHPT in our defined time period. Lastly, our data is reflective of a single tertiary center experience and may not represent the greater population.

Conclusion

Using a linear mixed model, accounting for repeated measures among patients, as well as patient level variance, renal insufficiency did affect IOPTH levels, with higher IOPTH in patients with CKD. However, it did not affect the change in IOPTH over time, and ultimately did not affect the likelihood of meeting the Miami

criterion. Therefore, IOPTH monitoring can still be confidently used in this patient population. Surgeons who routinely use normalization of PTH as an additional intra-operative criterion should note that patients with renal insufficiency make take longer to meet that goal, and additional time points should be collected. It is important to continue elucidating the factors that affect IOPTH kinetics, as intraoperative monitoring has implications on surgical decision-making.

COI/Disclosures

The authors have no related conflicts of interest to disclose.

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Figure Legends

Figure 1: Mean IOPTH at highest pre-excision value, followed by 5- and 10-minutes post-excision, IOPTH in pg/mL

Figure 2: Predicted IOPTH by linear mixed model, IOPTH in pg/mL

Tables

Table 1: Patient demographics, pre-, intra-, and post-operative variables (n=646)

Preoperative Variable	**All** (n= 646)		**Normal renal function** (n= 590)		**Chronic kidney disease** (n= 56)		**P value**
Age, years †	61	(52-69)	60	(52-68)	71	(64-77)	<0.001
Female	508	(78.6)	466	(79.0)	42	(75.0)	0.496
Ethnicity							0.423
White	495	(86.5)	448	(86.3)	47	(88.7)	
Black	46	(8.0)	43	(8.3)	3	(5.7)	
Hispanic	14	(2.5)	11	(2.1)	3	(5.7)	
Asian	11	(1.9)	11	(2.1)	0	(0)	
Other	6	(1.1)	1	(1.2)	0	(0)	
Biochemical Profile							0.052
Typical profile	460	(71.2)	427	(72.4)	33	(58.9)	
Normocalcemic	101	(15.6)	86	(14.6)	15	(26.8)	
Normohormonal	85	(13.2)	77	(13.1)	8	(14.3)	
Osteoporosis	171	(27.5)	156	(27.3)	15	(29.4)	0.672
Kidney stones	129	(20.0)	116	(19.7)	13	(23.2)	0.490
Preop Calcium, mg/dL	10.7	(10.4-11.2)	10.8	(10.4-11.2)	10.7	(10.3-11.2)	0.206
Preoperative iPTH, pg/mL	114	(82-160)	113	(82-160)	126	(81-169)	0.292
Preoperative 25-OH Vitamin D, ng/mL	31	(22-40)	31	(22-40)	33	(24-41)	0.276
Multi-gland disease‡	94	(14.6)	79	(13.4)	15	(26.8)	0.015
Postop Calcium, 6 mo, mg/dL	9.5	(9.2-9.8)	9.5	(9.2-9.8)	9.5	(9.3-9.8)	0.707
Postop iPTH, 6 mo, pg/mL	40	(28-51)	40	(27-51)	39	(31-54)	0.430
Postop Calcium, 1 yr, mg/dL	9.5	(9.2-9.7)	9.5	(9.2-9.7)	9.5	(9.3-9.8)	0.363
Postop iPTH, 1 yr, pg/mL	40	(30-49)	40	(30-49)	42	(33-49)	0.432

† All continuous variables expressed as median (interquartile range). All categorical variables expressed as n (percent). Percentages rounded to the nearest decimal, and therefore may not exactly equal 100.

‡ Multi-gland disease defined by the removal of more than 1 gland during parathyroidectomy. (iPTH= intact parathyroid hormone)

Table 2: Median intraoperative parathyroid hormone values of patients with biochemical cure at 6 months, pg/mL (interquartile range)

Time	Normal renal function (n= 574)	Chronic kidney disease (n= 53)	P value
Baseline	144 (99-213)	152 (101-244)	0.346
Time 0	126 (71-218)	143 (90-265)	0.132
5 minutes	58 (34-106)	76 (50-140)	0.015
10 minutes	37 (24-65)	54 (31-98)	0.004

Table 3: Univariable linear mixed model of intraoperative parathyroid hormone levels, with GFR (glomerular filtration rate) as a continuous variable†

Predictor Variable	Estimate	Standard Error	p-value
GFR	-0.007	0.003	**0.007**
Time			**<0.001**
0 minutes	ref	ref	ref
5 minutes	-1.111	0.120	<0.001
10 minutes	-1.451	0.120	<0.001
GFR*Time			**0.768**
GFR *0 minutes	ref	ref	ref
GFR *5 minutes	0.001	0.002	0.796
GFR *10 minutes	-0.001	0.002	0.645

†Rate of missingness = 4.0%

Table 4: Univariable linear mixed model of intraoperative parathyroid hormone levels, with GFR (glomerular filtration rate) as a categorical variable.†

Predictor Variable	Estimate	Standard Error	p-value
GFR			**0.006**
Chronic kidney disease (GFR< 60)	0.193	0.112	0.085
Time			**<0.001**
0 minutes	ref	ref	ref
5 minutes	-1.091	0.022	<0.001
10 minutes	-1.521	0.022	<0.001
GFR*Time			**0.077**
Normal renal function*time	ref	ref	ref
Chronic kidney disease *0	ref	ref	ref
Chronic kidney disease *5	0.105	0.076	0.165
Chronic kidney disease *10	0.166	0.074	0.025

†Rate of missingness = 2.6%

Table 5: Multivariable linear mixed model of intraoperative parathyroid hormone levels, with GFR (glomerular filtration rate) as categorical variable, all patients†

Predictor Variable	Estimate	Standard Error	p-value
Age	0.005	0.002	**0.032**
Male Sex	0.035	0.075	**0.643**
Race/Ethnicity			**0.678**
White	ref	ref	ref
Black	0.048	0.107	0.657
Hispanic	0.262	0.196	0.179
Asian	-0.109	0.220	0.621
Other	0.081	0.284	0.775
GFR			**0.016**
Chronic kidney disease	0.163	0.113	0.149
Biochemical Profile			**<0.001**
Typical	ref	ref	ref
Normocalcemic	-0.238	0.088	0.007
Normohormonal	-0.494	0.086	<0.001
Multi-gland disease	0.078	0.090	**0.385**

Time				**<0.001**
	0 minutes	ref	ref	ref
	5 minutes	-1.099	0.023	<0.001
	10 minutes	-1.516	0.023	<0.001
GFR*Time				**0.114**
	Normal renal function*time	ref	ref	ref
	Chronic kidney disease *0	ref	ref	ref
	Chronic kidney disease *5	0.123	0.076	0.107
	Chronic kidney disease *10	0.145	0.075	0.053

†Rate of missingness = 13.7%