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Secondary and Tertiary Hyperparathyroidism: The Utility of ioPTH Monitoring

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Abstract

Background—The aim of this study was to examine the utility of intraoperative parathyroid hormone (ioPTH) monitoring in patients with secondary (2) and tertiary (3) hyperparathyroidism (HPT).

Materials and methods—We identified 105 patients with 2HPT (n=33) and 3HPT (n=72) who underwent ioPTH monitoring during parathyroidectomy. Data are reported as mean $\pm$ SEM.

Results—The 2HPT patients underwent 17 subtotal, 10 total, and 6 re-exploratory parathyroidectomies, while 3HPT patients underwent 54 subtotal, 15 limited, and 3 re-exploratory parathyroidectomies. The percent decrease from the baseline ioPTH level at 5, 10, and 15 minutes after parathyroid resection respectively were $72 \pm 3\%$, $76 \pm 3\%$, and $76 \pm 3\%$ in patients with 2HPT, and $52 \pm 6\%$, $60 \pm 4\%$, and $69 \pm 4\%$ in patients with 3HPT. IoPTH levels failed to drop $>50\%$ from baseline in 5 patients (2HPT: n=2, 3HPT: n=3) who were normocalcemic at last follow-up. IoPTH did not alter the surgical approach in any 2HPT patients, but did alter management in 25% of 3HPT patients (15 limited resections and 3 supernumerary glands). Normocalcemia was achieved in 97% of 2HPT and 99% of 3HPT patients and 2 patients developed recurrent disease.

Conclusion—IoPTH levels fell by $>50\%$ in nearly 95% of patients with 2HPT and 3HPT, and reliably predicted post-operative cure. While the use of ioPTH did not alter surgical management in any patient with 2HPT, this rapid PTH assay impacted the surgical care of a quarter of the patients with 3HPT and may prove to be a useful adjunct in this group of patients.

Introduction

Secondary (2) and tertiary (3) hyperparathyroidism (HPT) are most often due to parathyroid gland hyperplasia and excess parathyroid hormone (PTH) secretion [1]. 2HPT occurs most commonly “secondary” to chronic renal failure (CRF) and is frequently referred to as renal HPT. As many as 90% of patients with CRF are reported to develop this disease by the time hemodialysis is initiated [2]. In combination, hyperphosphatemia and impaired renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol result in hypocalcemia. As a consequence of prolonged hypocalcemia, parathyroid chief cell hyperplasia occurs, PTH secretion increases, and skeletal resistance to PTH results in persistently, and often extremely, elevated PTH levels with renal osteopathy. The majority of patients with 2HPT are managed medically with calcium and vitamin D supplements, calcimimetics, phosphate binders, and vitamin D analogues, but approximately 1–2% of patients will require parathyroidectomy [1].

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3HPT is related to 2HPT in that 3HPT most commonly refers to persistently elevated PTH levels after renal transplant in patients with 2HPT and is observed in up to 30% of kidney transplant recipients [1,3]. However, 3HPT can develop after any long-standing period of hypocalcemia. After correction of the primary disorder (CRF by renal transplant), the hyperplastic parathyroid chief cells fail to resolute and continue to over-secrete PTH. Consequently, serum calcium levels are normal or even elevated in these patients because the hyperplastic glands function autonomously despite withdrawal of calcium and calcitriol therapy. In contrast to patients with 2HPT, the mainstay of treatment for patients with 3HPT is parathyroidectomy [3–6].

Over the last 20 years, several adjuncts have revolutionized the surgical management of patients with HPT [7–11]. Many of these techniques have been utilized in patients with 2 and 3HPT, but the efficacy of such applications is unclear. In particular, intraoperative PTH (ioPTH) measurement has been used in patients with both 2 and 3HPT [3,12–18]. However, unlike patients with primary HPT, surgery for either disease still requires bilateral neck exploration. Furthermore, in this patient population, ioPTH monitoring is complicated because of impaired renal function and delayed renal clearance of PTH. Conflicting results regarding the usefulness of ioPTH monitoring for 2 and 3HPT have been published [3,12–18]. Therefore, the purpose of this study was to examine the utility of ioPTH monitoring in patients with 2 and 3HPT.

Materials and Methods

We reviewed all patients with 2 and 3HPT who underwent parathyroidectomy between January 1984 and June 2008 by one of four surgeons at the University of Wisconsin Hospitals and Clinics (Madison, WI, USA). All patients with 2HPT had CRF as their underlying disease leading to HPT. Patients were considered to have 3HPT if they were previously diagnosed with 2HPT, underwent renal transplantation, and continued to have elevated intact PTH (iPTH) levels after normalization of renal function. Indications for parathyroidectomy in patients with 2HPT included calciphylaxis, patient preference, medical observation was not possible, or failure of maximal medical management, hypercalcuria, PTH >800 pg/ml, hyperphosphatemia (with calcium $\times$ phosphorus > 70), osteoporosis, or other symptoms (pruritis, pathologic bone fracture, ectopic soft tissue calcifications, severe vascular calcifications, or bone pain). Parathyroidectomy was undertaken in patients with 3HPT if the patients remained hypercalcemic (serum calcium >10.2 mg/dl) for more than one year after renal transplant, had severe hypercalcemia (serum calcium >12 mg/dl) at any point following transplant, or were symptomatic with hypercalcemia. In cases where enlargement of three or four glands was noted, a subtotal (3.5 gland) or total (4 gland) parathyroidectomy with auto-transplantation was carried out with cryopreservation of resected tissue. The intended parathyroid remnant size in these patients was the same for all surgeons at 50 to 75 mg. A limited resection was performed in 3HPT patients when only one or two of the four visualized parathyroid glands were enlarged. Histopathology and/or biopsy of parathyroids were not used to determine the type of resection to perform. A parathyroid gland was considered to be abnormally large if it was greater than approximately 50 mg. Patients had a transcervical thymectomy if preoperative imaging or intraoperative radioguided localization indicated that an intrathymic parathyroid was present, if an inferior gland was not discovered after a thorough exploration, or the patient had calciphylaxis.

Demographic and laboratory data were collected prospectively and analyzed retrospectively. All patients with 3HPT had undergone renal transplantation more than five months prior to parathyroidectomy, and were not currently undergoing dialysis. Our protocol for ioPTH measurements during parathyroidectomy was to draw a baseline ioPTH level prior to incision from a peripheral vein in an EDTA-containing test tube. After exploration and resection of all enlarged parathyroids, further ioPTH levels were drawn in the same fashion at 5, 10, and 15

minutes after excision. PTH levels were determined using the Elecsys 2010. Surgical success was defined as a normocalcemia (serum calcium less than or equal to 10.2 mg/dl) at 6 months or greater follow-up. Recurrence was considered to be a confirmed serum calcium level greater than 10.2 mg/dl at any time after 6 months.

For analysis of iPTH levels, patients were classified into CKD stage 1 to 5 by calculating their estimated creatinine clearance (eCrCl) with the Cockcroft and Gault formula which required weight in kilograms [19]. If a patient's weight was not available, the modified diet in renal disease (MDRD) equation was used to calculate the eCrCl [20]. The Kidney Disease Outcome Quality Initiatives (K/DOQI) clinical practice guidelines which define a target range of iPTH for each CKD stage were then used to classify iPTH levels as elevated if the measured postoperative value was outside the recommended iPTH range [21]. This adjustment of the goal postoperative iPTH level according to CKD stage was previously described by Triponez et al [22].

Descriptive statistics were used to summarize demographic and clinical characteristics of the 105 patients. Continuous data were compared by *t*-test, and categorical data by Chi-square or Fisher's exact test. Statistical analysis was performed using SPSS software version 10.0 (SPSS Inc; Chicago, IL). Data are reported as mean $\pm$ SEM. A *p* value of less than 0.05 was considered statistically significant, and *p* values were 2-tailed. Institutional Review Board approval was obtained for the data acquisition and analysis of the data.

Results

We identified 105 patients with 2HPT ($n=33$) and 3HPT ($n=72$) who underwent ioPTH monitoring during parathyroidectomy throughout the study period. The 2HPT patients underwent 17 subtotal, 10 total, and 6 re-exploratory parathyroidectomies, while the 3HPT patients underwent 54 subtotal, 15 limited, and 3 re-exploratory parathyroidectomies. In the patients with 2HPT, forearm implantation of a parathyroid remnant was performed in 5 of the total parathyroidectomies and 2 of the reoperative cases. For the 3HPT patients, all patients who underwent re-exploration (all after previous subtotal parathyroidectomy) had forearm autograft placement. The mean age of all patients was 50 ± 1 years, and 51% ($n=52$) were female. The average duration of follow-up was 28 ± 2 months for all patients. Table 1 depicts the demographic and follow-up data for each group. Patients with 3HPT were on average older than the 2HPT patients ($p<0.05$), but had a similar gender distribution. The duration of follow-up in the 3HPT patients also was longer when compared to 2HPT patients ($p<0.05$). Symptoms were present in 32 of the 33 (97%) patients with 2HPT and 55 of the 72 (76%) patients with 3HPT. The one asymptomatic 2HPT was refractory to maximal medical therapy. In addition, five patients with 2HPT were treated for calciphylaxis. The indication for surgery in the 17 asymptomatic 3HPT patients was persistent serum calcium elevation greater than 10.2 mg/dl for more than one year following renal transplantation.

Perioperative data including laboratory values, operative times, parathyroid gland weight, and length of stay also were examined. Table 2 demonstrates the mean preoperative and postoperative (measured greater than 6 months following surgery) serum calcium, iPTH, and creatinine levels of the patients. Several differences were observed between the 2 groups of patients which were consistent with their disease processes (Table 2). The mean parathyroid gland weight of the 2HPT patients (1333 ± 87 mg) was greater than the mean weight of the 3HPT patients (951 ± 95 mg, $p<0.05$). The duration of hospital stay for the 2HPT patients also was longer than that observed for the 3HPT patients (2.8 ± 0.8 vs. 1.1 ± 0.1 days, respectively, $p<0.05$).

Next, we evaluated the ioPTH dynamics in these patients. The mean baseline, 5, 10, and 15 minute ioPTH levels following parathyroid excision for the 2HPT patients were 995 ± 119 , 268 ± 42 , 240 ± 42 , and 243 ± 55 pg/ml, respectively. For the 3HPT patients, the average ioPTH measurements drawn at the same time points were 272 ± 25 , 110 ± 12 , 109 ± 24 , and 74 ± 7 pg/ml. The iPTH reference range in our laboratory during this study was 14–72 pg/ml. Thus, the mean ioPTH level for each group did not enter the normal reference range for this laboratory value within 15 minutes of parathyroid resection. However, at 5, 10, and 15 minutes following parathyroid resection, 29 (91%), 31 (94%), and 31 (94%) 2HPT patients, respectively, dropped below 50% of their baseline iPTH measurement. In the 3HPT patients, the number of patients who had their iPTH levels fall greater than 50% at these time points was 43 (60%), 55 (76%), and 64 (89%) patients, respectively. Figure 1 illustrates the ioPTH dynamics for the 2 and 3HPT patients expressed as a percentage of baseline PTH (drawn prior to skin incision in the operating room). This figure also demonstrates that a statistically significantly larger percent change in ioPTH levels was observed in 2HPT patients at 5 and 10 minutes post-excision when compared to 3HPT patients ($p < 0.05$). When applying the Miami criteria, 94% of patients with 2HPT had a 50% drop at 10 minutes, while 76% of 3HPT patients had the same drop.

Additional examination of ioPTH monitoring revealed that delayed ioPTH clearance (up to 25 minutes) was noted in 5 patients (7%) with 3HPT, but no patients with 2HPT. Thus, by 25 minutes post-excision 96% (69 of 72) of 3HPT patients had a 50% or greater drop in their ioPTH level. All patients with delayed ioPTH clearance and an eventual 50% drop in their levels were normocalcemic at last follow-up. However, ioPTH levels failed to drop more than 50% from the baseline level in 5 patients (2HPT: $n=2$, 3HPT: $n=3$) all of whom were normocalcemic at last follow-up. Therefore, for 2HPT patients, the false negative rate was 6%; whereas, for 3HPT patients, the false negative rate was 4%.

IoPTH did not alter the surgical approach in any patient with 2HPT, but did alter the approach in 25% of 3HPT patients, allowing for 15 limited resections and aiding in the identification of supernumerary glands in 3 cases. In patients with 2HPT, a subtotal or total parathyroidectomy was performed in all non-reoperative cases, and none of the 2HPT patients was found to harbor a supernumerary gland. Therefore, ioPTH monitoring did not affect the surgical procedure that was performed. However, for the 15 patients with 3HPT who underwent limited resection, ioPTH levels fell appropriately after the excision of only one ($n=9$) or two ($n=6$) enlarged parathyroids helping to confirm the adequacy of parathyroid resection. In these patients, a bilateral neck exploration was performed, and a limited resection of only the enlarged parathyroids (one or two of the four visualized glands) was carried out. IoPTH levels were then sent as described in the methods section. If the ioPTH level fell by more than 50% within 10 minutes of excision, then no additional parathyroid tissue was removed and the case completed. All 15 patients treated with a limited resection were normocalcemic at last follow-up. In the 3 cases of patients with 3HPT where supernumerary glands were present, the ioPTH level did not fall below 50% of baseline after excision of 3.5 glands. The continued ioPTH elevation led to further exploration which identified supernumerary glands in the mediastinum, thymus, and retroesophageal locations in these 3 patients. The continued exploration and identification of residual parathyroid tissue in these 3 patients was aided by the use of a radioguided probe. Thus, 18 of the 72 patients with 3HPT (none of whom were re-explorations) had their surgical management affected based on the results of ioPTH monitoring.

In addition to analyzing ioPTH monitoring, we evaluated the outcomes of the patients in terms of both complications and surgical cure. The overall complication rate in this series was 3.8%. One patient with 2HPT died due to complications of calciphylaxis. In addition, three patients with 3HPT had complications: one with permanent hypocalcemia, one with pneumonia, and one with a RLN injury. Normocalcemia (at a minimum of 6 months post-operatively) was achieved in 97% of 2HPT ($n=31$) and 99% of 3HPT ($n=71$) patients. Two patients, one with

2HPT and the other with 3HPT, developed recurrence of their disease at more than 6 months following their initial parathyroidectomy. Both patients initially underwent a subtotal parathyroidectomy with resection of 3 and ½ glands and had a greater than 50% drop in their ioPTH levels at 5 minutes post-excision. Recurrence was due to remnant hyperplasia in both cases. When we examined iPTH levels in these patient, the iPTH levels exceeded the adjusted normal target iPTH range in 27% and 46% of 2HPT ($n=9$) and 3HPT ($n=33$) patients, respectively, at anytime postoperatively. Therefore, these numbers reflect the total number of patients with either persistent iPTH elevation (<6 months) or recurrent iPTH elevation (>6 months). No patients had both elevated serum calcium levels and elevated iPTH levels.

Discussion

Surgery for all types of hyperparathyroidism (HPT) has been associated with minimal morbidity and excellent cure rates when performed by experienced surgeons [9,23–28]. Several adjuncts that have contributed to safe and successful parathyroidectomies in patients with primary HPT have been applied to patients with secondary (2) and tertiary (3) HPT as well [3,6,17,18,23,24,27,29]. The focus of this investigation was the utility of one of these adjuncts, intraoperative PTH (ioPTH) monitoring. This technique has been used with varying success rates in patients with both 2 and 3HPT [3,12–16,18,30]. However, unlike patients with primary disease, parathyroidectomy for 2 and 3HPT should not be performed with a minimally invasive approach and requires a bilateral neck exploration. Furthermore, the underlying renal failure in patients with 2 and 3 HPT can lead to delayed renal clearance of PTH. Currently, no consensus has been made over the use of ioPTH monitoring in 2 and 3HPT patients. In this study, ioPTH levels fell by more than 50% in at least 94% of patients with 2HPT and 3HPT by 25 minutes post resection and reliably predicted post-operative cure. While ioPTH monitoring did not change the surgical management of any patient with 2HPT, rapid PTH testing did influence the operative care of 25% of the 3HPT patients.

Despite advances in medical and surgical treatment, the incidence of 2 and 3HPT is on the rise in the United States and elsewhere because of the increasing incidence and prevalence of CRF [31]. While the incidence of 3HPT is still low, the number of patients presenting for surgery is increasing as greater numbers of patients are successfully transplanted and diagnosed with 3HPT. Furthermore, the growing awareness of osteoporosis and other consequences of 3HPT have led previously conservative practices to be replaced with referral for parathyroidectomy. For patients with 3HPT, parathyroidectomy remains the only curative treatment option [1,3, 6]. In this study, 76% of the 3HPT patients had symptoms of bone pain and/or significant osteoporosis/osteopenia. We have continued to recommend an aggressive approach for patients with 3HPT emphasizing early referral for consideration of parathyroidectomy. In addition, even though novel methods for medically treating patients with 2HPT have been introduced, surgical intervention is still necessary at times in these patients with approximately 1–2% of patients with 2HPT requiring parathyroidectomy each year [1].

Classically, 3HPT is due to hyperplasia of all four glands, though some studies suggest that over 20% of 3HPT patients may have single or double adenomas as the underlying pathology [5,32]. Whether these cases represent post-transplant patients in whom sporadic primary HPT (adenomas) has developed or resolution of autonomous function in all but one or two glands is unclear. The etiology of 3HPT in this subset of patients may also result from asymmetric hyperplasia [5]. In our current investigation, approximately 21% of 3HPT patients were found to have enlargement of only one or two parathyroid glands at the time of surgery. In these 15 cases, the ioPTH assay supported a limited resection of only the enlarged glands, and all of these patients were cured in long-term follow-up. Since all of the patients with 2HPT had symmetric enlargement of all visualized parathyroids, the rapid ioPTH assay was not able to

be utilized in a similar manner. To the best of our knowledge, hyperplasia of only one or two parathyroids has not been reported in 2HPT patients.

While ioPTH testing has no apparent role with respect to limited resection in patients with 2HPT, conflicting results regarding the general usefulness of ioPTH monitoring for 2HPT have been published [12–15]. Studies have shown that ioPTH testing depends on renal function and PTH assay specificity [12–14]. However, studies differ in their definition of successful parathyroidectomy. When a 50% drop from the baseline ioPTH is considered predictive of sufficient parathyroid tissue resection, these investigations support the utility of ioPTH monitoring in patients with 2HPT. Our investigation confirms these studies and demonstrated that 94% of patients with 2HPT will drop their PTH level more than 50% of the baseline within 10 minutes of parathyroid resection. However, the mean PTH level of 2HPT patients at 10 minutes was 240 ± 42 pg/ml which, individually, may be above the K/DOQI guidelines for “normal” PTH levels by CKD stage. At minimum of 6 months follow-up, the rates of normocalcemia and normal PTH levels (for CKD stage) in the 2HPT patients were 97% and 73%, respectively. Whether or not similar outcomes would be observed without ioPTH monitoring is speculative since no comparison group was included in this study. However, the literature suggests that comparable results are obtainable without ioPTH monitoring [4,6,29,30,32–35]. Moreover, no 2HPT patients had their surgical approach altered due to findings in the ioPTH monitoring. We also observed no delayed clearance of PTH in the 2HPT patients in the current investigation, though reports indicate that depending upon the specificity of the PTH assay, an adequate drop in ioPTH levels (>50%) may not be seen for up to 30 minutes after curative resection (because of CRF and delayed PTH clearance) [12–14]. Our results did show that 2HPT patients had a greater percent decrease in their ioPTH levels at 5 and 10 minutes post-resection when compared to 3HPT patients. This finding is likely because the 2HPT patients had significantly higher baseline PTH levels.

While the utility of ioPTH monitoring in 2HPT patients is questionable, for patients with 3HPT, ioPTH testing has been found to be more beneficial [3,15,18,36,37]. However, the ioPTH criteria that are predictive of cure in these patients are disputed. Applying the traditional Miami criteria proposed for patients with primary HPT (>50% ioPTH drop at 10 minutes) has previously been shown to afford a 94% or greater sensitivity in patients with 3HPT which was confirmed in this study [3,18]. We observed that only 76% (55 of 72) of 3HPT patients strictly met the Miami criteria at 10 minutes, and the sensitivity for predicting cure in these 55 patients was 98%. However, by 25 minutes, 96% (69 of 72) of patients had dropped their PTH level more than 50% of baseline, and, for these 69 patients, the ioPTH sensitivity was 99%. Therefore, application of the Miami criteria (50% drop in ioPTH) in 3HPT patients appears to be efficacious in the majority (76%) of 3HPT patients, although in a portion of these patients it may take longer than ten minutes to reach this criteria. Application of a cutoff PTH level for predicting curative resection in 3HPT patients, as opposed to a percent decrease from baseline, also has been proposed. The basis of this cutoff value is derived from literature in patients with primary HPT from hyperplasia (multigland disease) that demonstrates that a final ioPTH level of less than 35 pg/ml or a greater than 90% drop from baseline is predictive of cure about 90% of the time [37]. The logic follows that perhaps a cutoff ioPTH value should be utilized in patients with multigland disease from any etiology. In patients with 3HPT, Milas and Weber have proposed that a target ioPTH level less than 200 pg/ml predicts curative resections, while others support an ioPTH level less than 65 pg/ml [15,36,37]. Lack of consensus guidelines for ioPTH monitoring in patients with 3HPT and skepticism over the potential impact on the overall success rate of parathyroidectomy has led some groups to abandon the routine use of this adjunct [18]. Though a previous investigation from our group reported that ioPTH impacted operative management in 16% of cases [3]. In the current series, the percent of patients impacted by ioPTH testing increased to 25%. Thus, we continue to support the use of ioPTH monitoring in this group of patients.

In conclusion, application of the Miami criteria, a decrease in ioPTH levels by greater than 50% at 10 minutes after adequate parathyroid resection, appears to reliably predict postoperative cure in patients with 2 and 3HPT. However, monitoring of ioPTH levels for up to 25 minutes may be needed in this population to observe the appropriate (>50%) drop in PTH levels due to poor renal function. In this series, the use of ioPTH did not alter the surgical management of any patients with 2HPT, but did impact the management of 25% of the patients with 3HPT. Therefore, the utility of ioPTH testing in 2HPT remains to confirm the adequacy of resection, but does confer additional costs to the patients. Theoretically, ioPTH monitoring will help identify patients with 2HPT and a supernumerary gland. However, due to the rarity of these two entities, we were unable to confirm the usefulness of ioPTH in such a setting. Conversely, these data do support the role of ioPTH monitoring in the intraoperative management of patients with 3HPT and appears to be a useful adjunct in this group of patients. Nonetheless, in patients with 2 and 3HPT, consensus is needed over the definitions of cure and recurrence in terms of PTH levels.

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Fig. 1.

This graph expresses the ioPTH levels as a percentage of the baseline level at 5, 10, and 15 minutes after parathyroid resection. In patients with 2HPT (solid black line), the respective decreases from baseline were 72 ± 3 , 75 ± 3 , and $76 \pm 3\%$. For patients with 3HPT (grey dashed line), the decreases were 52 ± 6 , 60 ± 5 , and $69 \pm 4\%$.

Table 1

Patient demographics and follow-up

	2HPT	3HPT
<i>N</i>	33	72
Age (yrs)	45 ± 3	53 ± 2*
Female (%)	15 (46)	37 (51)
Follow-up (mos)	21 ± 4	33 ± 3*

2HPT, secondary hyperparathyroidism; 3HPT, tertiary hyperparathyroidism.

*
 $p < 0.05$

Table 2

Patient laboratory data

	2HPT (n=33)	3HPT (n=72)
Preoperative		
Calcium (mg/dl)	9.8 ± 0.2	11.0 ± 0.1 *
iPTH (pg/ml)	1131 ± 148	294 ± 28 *
Creatinine (mg/dl)	7.5 ± 0.8	1.5 ± 0.1 *
Postoperative		
Calcium (mg/dl)	9.0 ± 0.2	9.2 ± 0.1
iPTH (pg/ml)	113 ± 36	53 ± 5 *
Creatinine (mg/dl)	7.0 ± 0.8	2.1 ± 0.3 *

2HPT, secondary hyperparathyroidism; 3HPT, tertiary hyperparathyroidism; iPTH, intact parathyroid hormone.

Reference serum calcium range: 8.5–10.2mg/dl

Reference iPTH range:14–72 pg/ml

*
p<0.05