Hindawi Publishing Corporation
Journal of Osteoporosis
Volume 2012, Article ID 914214, 6 pages
doi:10.1155/2012/914214

Clinical Study

A 10-Year Experience in Intraoperative Parathyroid Hormone Measurements for Primary Hyperparathyroidism: A Prospective Study of 91 Previous Unexplored Patients

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Received 1 November 2011; Accepted 18 December 2011

Academic Editor: Markus J. Seibel

Introduction. Primary hyperparathyroidism (PHP) is characteristically determined by high levels of calcium and high or inappropriate levels of parathyroid hormone (PTH). Technological advances have dramatically changed the surgical technique over the years once intraoperative parathyroid hormone (IOPTH) assay had allowed for focused approaches. *Objective*. To evaluate our 10-year experience in employing a rapid intraoperative PTH assay for PHP. *Methods*. A prospective cohort of 91 PHP-operated patients in a tertiary institution in São Paulo, Brazil, from June 2000 to April 2011. *Results*. We had 85 (93.4%) successful parathyroidectomies, 6 (6.6%) failed parathyroidectomies in 91 previous unexplored patients, and 5 (100%) successful remedial surgeries. The IOPTH was true-positive in 88.5%, true-negative in 7.3%, false-positive in 2.1%, and false-negative in 2.1% of the procedures. IOPTH was able to obviate additional exploration or to ask for additional exploration in 92 (95.8%) procedures. *Conclusion*. The IOPTH revealed to be an important technological adjunct in the current parathyroid surgery for PHP.

1. Introduction

Primary hyperparathyroidism (PHP) is a hypercalcemic disease stemming from an abnormal increase in parathyroid hormone (PTH) secretion by one or more parathyroid glands. The hallmark of this condition is the presence of high levels of calcium and high or inappropriate levels of PTH. Primary hyperparathyroidism is more common in women than in men and increases with aging in both genders [1]. Since primary hyperparathyroidism was first described, surgery remains the only definitive therapy [2]. The goal of parathyroidectomy is the excision of the abnormal parathyroid gland(s), preserving the normal ones in order to achieve and maintain a postoperative normocalcemic state [3]. Success rates for surgical treatment depend on the skill and experience of the surgeon in finding and recognizing the pathologic changes and excising the correct amount of hyperfunctioning parathyroid tissue [4].

The surgical treatment of PHP has undergone substantive changes since the first successful parathyroidectomy was performed by Felix Mandl in 1925 [5]. It is now expected that the vast majority of patients will be cured during initial surgical exploration at a low probability of morbidity. The conventional time-honored operation employing general endotracheal anesthesia and bilateral cervical exploration is safe and effective when performed by experienced surgeons. However, recent technical innovations, including improved preoperative localization and availability of rapid intraoperative PTH assays (IOPTH), have yielded focused approaches with excellent outcomes.

Sporadic primary hyperparathyroidism is caused by a single enlarged parathyroid gland (parathyroid adenoma) in approximately 85% of the cases, whereas multigland hyperplasia occurs in 15% and parathyroid carcinoma is found in less than 1% of patients. Unlike the previous dogma that required surgical identification of both enlarged and normal parathyroid glands, the current paradigm in many centers is to identify and excise the incident enlarged gland and to confirm operative cure, employing a rapid intraoperative PTH assay. Due to the relatively short half-life of PTH (4-5 min), a dramatic drop in circulating hormone can be detected once the abnormally secreting gland or glands have been removed [6]. A curative drop in PTH allows the surgeon to terminate the operation and obviate additional exploration, whereas failure of the PTH levels to demonstrate an adequate decrement asks for additional exploration because of the presence of presumed additional hypersecreting gland(s).

The aim of the present study was to evaluate our 10-year experience in employing a rapid intraoperative PTH assay for PHP.

2. Patients and Methods

2.1. Study Design. This is a prospective study on a cohort of operated patients treated at a university referral center.

This investigation was approved by the UNIFESP/EPM Ethics Committee.

2.2. Patients. From June 2000 to April 2011, 96 surgeries for PHP were performed at Hospital São Paulo UNIFESP/EPM, São Paulo, Brazil. These 96 procedures were performed in 91 previous unexplored patients who had at least 6 months of postoperative follow-up with enough reported data to be eligible for the study. The remaining 5 were remedial procedures.

The PHP diagnoses were established in the presence of high levels of calcium and high or inappropriate levels of PTH.

All patients had their age, gender, symptoms (bone and kidney), preoperative localization tests, serum ionized calcium (iCa), serum total calcium and intact PTH recorded before parathyroidectomy, as well as IOPTH dosages. The laboratorial tests were repeated 1 month, 6 months, and in 1-year increments after surgery.

2.3. Methods. A series of 91 consecutive patients with primary hyperparathyroidism underwent parathyroidectomy guided by intraoperative PTH at Federal University of São Paulo, Brazil, from June 2000 to April 2011. Focused parathyroidectomy guided by intraoperative PTH was the initial procedure when preoperative localization tests were positive and when there were no suspicion of malignant disease. A bilateral cervical exploration guided by intraoperative PTH was performed when preoperative localization tests were negative.

A baseline peripheral venous blood sample was obtained just after anesthesia induction as well as 10 minutes after the abnormal parathyroid tissue removal. The intraoperative criterion used to predict successful parathyroidectomy was a decrease in the intact PTH levels exceeding 50% from the preincision hormone level [7]. If this criterion was met, surgical exploration of the neck would be completed and the incision closed. Otherwise, further surgical exploration of the neck would have to be carried on.

Intraoperative PTH was measured using Elecsys PTH Immunoassay (Elecsys 1010 System, Roche, Mannheim, Germany). The test is an immunometric assay based on monoclonal antibodies, magnetic particles as solid phase, and ruthenium complex as chemiluminescent label. Total time to perform the assay is 9 minutes; reference values are 10–65 pg/mL. To validate the rapid PTH assay, 170 samples from the study were also measured using a standard immunofluorimetric assay (IFMA) [8].

Table 1: Demographic, clinical, and biochemical aspects in 91 patients, with PHP.

Variable	
Patients	91
Age, mean (range) y	54 (12–80)
Gender, N°. (%)	
Male	18 (19.8)
Female	73 (80.2)
Symptoms, N°. (%)	
none	13 (14.3)
Kidney stones	47 (51.6)
Osteoporosis	37 (40.7)
Pathologic bone fracture	4 (4.4)
Renal disease related to PHP	4 (4.4)
Biochemical	
iCa, mean (range) mmol/L	1.64 (1.37–2.50)
tCa, mean (range) mg/dL	12.0 (10.5–19.3)
iPTH, mean (range) pg/dL	425.6 (74–2605)

Reference: iCa: 1.15–1.32 mmol/L; tCa: 8.5–10.5 mg/dL; PTH 11–65 pg/dL.

The IOPTH accuracy calculation was based on the following definitions: a true-positive (TP) result of IOPTH was defined as the correct prediction of postoperative normal calcium levels for at least 6 months; true negative (TN) was the correct prediction of incomplete excision by either resection of an additional gland(s) or operative failure; false positive (FP) was the incorrect prediction of normocalcemia with subsequent postoperative persistent hypercalcemia and high PTH levels; false negative (FN) was the incorrect prediction of incomplete excision followed by postoperative normocalcemia.

We considered cured patients that presented normocalcemia along the postoperative follow-up. Persistent disease was considered when serum calcium and PTH levels remained above normal range just after surgery. Recurrence was defined when, after reaching normocalcemic levels, serum calcium and intact PTH measurements start to rise to abnormal values at least 6 months after surgery.

Serum Ionized calcium (1.15–1.32 mmol/L), serum total calcium (8.5–10.5 mg/dL) and intact PTH (11–67 pg/mL), were measured using standard automatic assays.

3. Results

The demographic, clinical, and biochemical aspects of 91 patients with PHP are shown in Table 1.

Among all cohort of 91 patients, 69 (75.8%) had solitary adenoma, 10 (11.0%) had Multiple Endocrine Neoplasia Type 1 (MEN1), 6 (6.6%) had double adenomas, 4 (4.4%)

Table 2: Outcomes in 91 PHP patients.

Variable	Operative success	Operative failure
Total	85	6
Solitary adenoma	69	0
Double adenoma	4	2
MEN1	8	2
Carcinoma	3	1
Waiting for remedial surgery (MGD)	1	1
Biochemical		
iCa, mean (range) mmol/L	1.64 (1.35–2.50)	1.68 (1.51–2.06)
tCa, mean (range) mg/dL	12.0 (10.5–19.3)	12.0 (10.6–13.4)
iPTH, mean (range) pg/dL	431.5 (80–2605)	332.0 (74–1155)
Intraoperative results		
IOPTH mean decay (range)%	80.5 (34.3–96.0)	50.5 (32.4–84.1)
IOPTH true-positive, N° (%)	80 (87.9)	0
IOPTH true-negative, N°, (%)	3 (3.3)	4 (4.4)
IOPTH false-positive, N°, (%)	0	2 (2.2)
IOPTH false-negative, N°, (%)	2 (2.2)	0

had carcinomas, and 2 (2.2%) patients are still waiting for remedial surgery for multiglandular disease (MGD), 1 of whom had recurrence disease after 10 years of follow-up and the other persistent disease after a false positive IOPTH (Table 2).

We had 85 (93.4%) successful parathyroidectomies 6 (6.6%) failed parathyroidectomies in 91 previous unexplored patients, and 5 (100%) successful remedial surgeries. Among the 85 successful patients, 69 (81.2%) had solitary adenoma, 3 (3.5%) had carcinoma, 4 (4.7%) had double adenomas, 8 (9.4%) had MEN1, and 1 (1.2%) still has MGD (Table 2).

The mean decay of IOPTH in the successful group of patients was 80.5% (34.3% to 96.0%). In these 85 patients, we had 80 TP results (67 adenomas, 3 carcinomas, 8 MEN1 and 2 recurrences—these last two patients shown in Table 3). We also had 3 cases of double adenoma in which the IOPTH resulted in a TN value, requiring additional exploration to prevent persistent disease (Table 2). There were only 2 FN results among the successful group patients (Table 4). The mean decay of IOPTH in the 80 patients with TP results was 81.7%, with a minimum drop of 55.0% (55.0% to 96.0%).

Operative failure of the initial surgery occurred in 6 patients: 2 Double Adenoma, 2 MEN1, 1 Carcinoma, and 1 MGD who is still waiting for remedial surgery (Table 5). Both cases of Double Adenoma had a TN decay of IOPTH, but the second adenoma wasnot found during the initial operation. With the aid of new localization exams, successful remedial operations were performed with an IOPTH TP result.

The patient with parathyroid carcinoma developed hypercalcemia and high levels of PTH two months after surgery. In search of distant metastasis, this patient underwent a pulmonary computerized tomography and multiple pulmonary nodules were found. For this reason, she was classified as IOPTH false-positive.

In both MEN1 patients, the IOPTH showed an incomplete resection of all hyperfunctioning parathyroid tissue with TN results. One patient already had MEN1 diagnosis at the time of initial surgery and we failed to find the fourth gland. The other patient was first operated as a solitary adenoma and MEN1 diagnosis surfaced just in the follow-up.

There was only one case in the operative failure patients; the IOPTH had an FP result (Table 4).

4. Discussion

The surgical treatment for primary PHP has undergone some changes in recent years, evolving from the standard bilateral neck exploration technique to a less time-consuming procedure of unilateral neck exploration. Taking into account the increasing number of asymptomatic and/or oligosymptomatic primary hyperparathyroidism diagnosis in the recent years, the need for a safe and less time-consuming procedure with low perioperative morbidity is clear. Preoperative parathyroid localization imaging study and IOPTH are essential components of the focused parathyroidectomy that allow the excision of all abnormal parathyroid glands without the examination of the normally secreting glands [9]. The clinical utility of rapid IOPTH measurements in parathyroidectomy was first reported in 1988 using a modified intact PTH IRMA assay [10]. Since then, rapid assays have been developed by means of radioactive [4, 11, 12] as well as nonradioactive formats [12, 13]. The predominance of a solitary adenoma disease in 85% to 96% of cases of PHP and the short half-life of intact PTH (1–84) of only 1.4 to 4 minutes [14–20] combined with the remaining suppressed normal parathyroid glands after removal of all hyperfunctioning tissue [15] allows the measurement of IOPTH to evaluate its decline rates. Several studies have demonstrated the utility of IOPTH monitoring in the treatment of single-gland primary hyperparathyroidism [3, 8, 21–27]. Most experts agree that IOPTH assay is the most useful intraoperative adjunct to assist the surgeon in PHP surgical treatment [28, 29]. It is worth highlighting the useful employment of preoperative localization imaging study in conjunction with IOPTH: the former points out where the surgeon should start exploration from, and the latter assures that hypersecretory parathyroid tissue removal was accomplished.

The current usual criteria for IOPTH measurement describe a decrease of 50% or over from either the baseline (preincision) [7] or the highest preincision or preexcision [24] value within 10 minutes following hyperfunctioning parathyroid resection, pointing out surgical cure and predicting normocalcemia [30]. By resorting to those criteria, high accuracy in intraoperative prediction of cure is achieved [30]. Mostly for practice and cost reasons, we have used just two samples as our criteria since we started making use of the IOPTH: the preincision and 10 minutes postexcision of hyperfunctioning parathyroid.

Table 3: Recurrence cases among the successful true-positive IOPTH patients.

Patient	Initial surgery						Remedial					
	Ultra sound	Sesta mibi	N° glands excised	IOPTH decay	Follow-up	IOPTH result	Ultra sound	Sesta mibi	N° glands excised	IOPTH decay	Follow-up	Diagnosis
F, 59 y	Neg	Right	1	88.4	Recurrence at 48 months	TP	Left	Left	1	78.4	12	Double adenoma
F, 52 y	Neg	Left	1	80.5	Recurrence at 118 months	TP	Right	Right	Waiting remedial surgery			MGD

Table 4: False results of IOPTH.

Patient	Biochemical			Localization tests		Surgical findings	IOPTH			Decision	IOPTH results
	tCa	iCa	PTH	Ultrasound	Sestamibi		Preinc	Postex	Decay		
M, 40 y	12.6	1.94	455	Right	Right	Cystic Adenoma	798	524	34.3%	Rupture of the cyst	FN
F, 62 y	12.8	1.68	181	Neg	Left	Solitary Adenoma	209	116	44.5%	Bilateral dissection with 3 normal glands	FN
F, 59 y	10.6	1.52	159	Right	Right	Solitary Adenoma	216	106	50.9%	End of procedure	FP
F, 62 y	13.4	2.60	2800	Right	Right	Carcinoma	2480	394	84.1%	End of procedure	FP

Preinc: preincision; postex: postexcision; FN: false-negative; FP: false-positive.

Table 5: Cases of operative failure.

Patient	Initial surgery				IOPTH result	Remedial					
	Ultra sound	Sesta mibi	N° glands excised	IOPTH decay		Ultra sound	Sesta mibi	N° glands excised	IOPTH decay	Follow-up	Diagnosis
M, 26 y	Left	Neg	1	42.4	TN	Right	neg	1	89.4	126	Doublé Adenoma
F, 38 y	Neg	Neg	1	32.4	TN	Right	neg	1	89.4	54	Doublé Adenoma
F, 32 y	Neg	Right	1	33.5	TN			3	70.3	78	MEN1
M, 22 y	Neg	Neg	3	51.6	TN		Right	1	85.4	84	MEN1
F, 62 y	Right	Right	1	84.1	FP					36	Carcinoma
F, 59 y	Right	Right	1	50.9	FP		Neg	waiting remedial surgery			MGD

Neg: negative; TP: true positive; TN: true negative; FP: false positive; MGD: multiple glandular disease; MEN1: multiple endocrine neoplasia type 1. Decay values are in %; follow-up period in months.

Our series of 96 PHP consecutive surgeries over 10 years reflects a complex tertiary referral center and has its limitations. The data are subject to selection and referral bias. Most of these patients were referred specifically due to their severe signs/symptoms and comorbid medical conditions, which are related to their high bone and kidney disease and the 4.4% incidence of carcinoma. Furthermore, all patients were first evaluated by an endocrinologist group specialized in osteometabolic disease who elected the patients for surgical treatment, reflecting the 11% incidence of MEN1 and the absence of familial hypocalciuric hypercalcemia case in our surgical series.

The PHP diagnose has not been made in a routine practice in most Brazilian centers, and many patients have their diagnoses made just after severe signs/symptoms. We have noticed an increase in the percentage of asymptomatic patients over the years in the number of PHP cases [31], but probably such increase has not been enough to raise the number of our small solitary adenomas (78.3%).

We get an inferior number of successful parathyroidectomy (93.4%) in previous unexplored patients compared to some large series [9, 32], but it can be considered a satisfactory result, taking into account the high number of patients with carcinoma and MEN1 in our series. On the other hand, we have obtained good results (100%) in 5 successful second surgical explorations so far: first, we removed a second adenoma in three patients (two persistent and one recurrent disease); second, we were able to remove a not found fourth gland in a MEN1 patient, and finally, we removed three glands in a MEN1 patient previous operated as an sporadic PHP.

In our series of 91 patients, IOPTH had true results in 87 patients (95.6%). However, considering our 96 surgical procedures (5 remedial surgeries), IOPTH was able to obviate or to ask for additional exploration because of the presence of presumed additional hypersecreting gland(s) in 92 (95.8%) procedures.

The IOPTH had a mean decay of 81.7% in the TP patients, and the minimum drop in our series that results in patient cure (operative success) was 55.0%. We had only 4 IOPTH false results, 2 FP and 2 FN.

The 2 FN results were followed by unnecessary bilateral neck dissection. One of these cases occurred in a ruptured parathyroid cystic adenoma that may have resulted in a substantial elevation of the hormone levels after the preincision sample, and it should be related to an inadequate IOPTH decay [19]. The second patient had the others three parathyroid glands identified in normal conditions. Based on such scenario, surgical procedure was ended and the patient evolved with normocalcemia.

One FP case occurred in a patient with concordant preoperative localization tests. The IOPTH decay was 50.9%, dropping from 216 pg/dL to 106 pg/dL. As observed by other authors, the FP cases are usually represented by a marginal PTH level decrease with a final PTH level above the normal range [9]. For these reasons, stricter criteria for the IOPTH dynamics have been suggested, such as the return of the 10-minute PTH to within normal range [7]. However, these stricter criteria were estimated to increase the operative success only by 0.3% [9], with significant increase in the false negative results, bringing on more unnecessary bilateral neck dissection [9, 33]. Using these stricter criteria in our patients would have brought about 21 (24.7%) unnecessary bilateral dissections, and just one additional diagnose.

We classified a patient with parathyroid carcinoma that revealed metastatic pulmonary disease two months after surgery as an FP result because she certainly had metastatic disease at the surgery and IOPTH (84.1% decay) failed to predict the presence of presumed additional hypersecreting tissue. However, it can be controversial to suppose that IOPTH has failed in this patient, once IOPTH was not defined to predict distant disease.

All 4 patients with parathyroid carcinoma had very suggestive signals of malignant disease at presentation (very high PTH levels, severe hypercalcemia and palpable neck mass) and were not elected to the focused approach. They were submitted to an "en bloc" tumor resection, removing the parathyroid tumor, the ipsilateral thyroid lobe, and the lymph nodes related to a central neck dissection.

During the follow-up period, 2 (2.1%) patients presented PHP recurrence, 48 months and 118 months after initial parathyroidectomy. One patient removed a second adenoma and had a successful remedial surgery with IOPTH decay of 78.4%. The second patient recurrence occurred almost 10 years after initial surgery and is still waiting for remedial surgery. Udelsman et al. [32] published a large series of 1,650 PHP patients and found 5 (0.3%) recurrent cases. Other authors have published higher recurrence rates, reaching up to 4.1% [34]. The reason of this recurrence phenomenon is yet to be further explored. One of our series limitations is the absence of vitamin D dosages, one important factor that should be related to the genesis of PHP recurrence.

5. Conclusion

The IOPTH revealed to be an important technological adjunct in the current parathyroid surgery for PHP.

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