

Intraoperative Parathyroid Hormone Assay in Patients With Primary Hyperparathyroidism and Double Adenoma

Emad Kandil, MD; Haytham H. Alabbas, MD; Anshuman Bansal, MS; Tareq Islam, MD; Anthony P. Tufano, MD; Ralph P. Tufano, MD

Objective: To determine the utility of parathyroid hormone (PTH) monitoring for double adenomas (DAs).

Design: Retrospective chart review.

Setting: Tertiary referral center.

Patients: The study included 47 patients with primary hyperparathyroidism who had DAs identified during first-time parathyroid exploration.

Main Outcome Measures: Intraoperative PTH levels were measured in every case, and the intraoperative PTH assay and its influence on surgical outcome were examined.

Results: A total of 47 of 552 consecutive patients (8.5%) with primary hyperparathyroidism were found to have DAs; 457 patients (82.7%) had single adenomas; and 48 patients (8.6%) had disease in more than 2 glands. The mean (SD) age of the patients with DAs was 58 (14) years,

and 26 patients (55%) were female. The mean (SD) preoperative intact PTH level was 129 (57) pg/mL (to convert to nanograms per liter, multiply by 1), and the preoperative serum calcium level was 11.0 (0.6) mg/dL (to convert to millimoles per liter, multiply by 0.25). In all patients, the intraoperative PTH levels decreased by 79.7% (11.4%) from baseline after removal of both abnormal parathyroid glands. When the location could be confirmed, the second adenoma was ipsilateral in 17 patients (36%) and contralateral in 27 patients (64%). The mean (SD) postoperative intact PTH level was 46 (26) pg/mL at 6 months, and the cure rate was 98%.

Conclusions: Intraoperative PTH monitoring and maintenance of normocalcemia after surgery confirm previous reports that DAs do exist and are not simply missed cases of 4-gland hyperplasia. Intraoperative PTH monitoring accurately predicted the success of parathyroidectomy in 98% of patients with DAs.

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PRIMARY HYPERPARATHYROIDISM (PHPT) is a common endocrine disorder, with approximately 100 000 new cases diagnosed each year in the United States.¹ It is caused by a single adenoma in 87% to 91% of the cases. The remaining cases are 4-gland hyperplasia, double adenomas (DAs), and, much less commonly, parathyroid carcinoma. Double adenomas have been reported to occur in 2% to 15% of patients undergoing operation for PHPT.²⁻⁶ Nonetheless, the very existence of parathyroid DAs is still controversial.^{2,7} Some investigators have suggested that DAs do not exist and instead represent cases of asymmetrical 4-gland hyperplasia.⁸ For others, a DA is a recognized clinical entity of PHPT.^{3,5,9}

Parathyroidectomy is the only curative treatment for PHPT that resolves metabolic complications and improves symptoms and quality of life.¹⁰ To identify and

remove the enlarged, hyperfunctioning parathyroid glands, many surgeons now use minimally invasive, targeted parathyroidectomy instead of traditional bilateral neck surgical exploration.¹¹ Limited neck surgical exploration approaches for parathyroidectomy have been successfully used, mainly because of better preoperative localizing studies that allow accurate identification of the enlarged parathyroid glands. Furthermore, measurement of intraoperative parathyroid hormone (IOPTH) levels to detect a decrease greater than 50% in the intact PTH (iPTH) levels and into the normal range can be used to predict a biochemical cure in most patients.^{12,13} The use of limited surgical exploration for parathyroidectomy depends on the ability to reliably select those patients who have PHPT due to single-gland disease. The percentage of patients who undergo limited neck surgical exploration for parathyroidectomy ranges from 39% to 70% of all patients with

Author Affiliations:

Department of Surgery, Tulane University School of Medicine, New Orleans, Louisiana (Drs Kandil, Alabbas, and Islam); and Departments of Otolaryngology–Head and Neck Surgery (Mr Bansal and Dr Tufano) and Surgery (Dr Tufano), Johns Hopkins School of Medicine, Baltimore, Maryland.

PHPT.¹⁴⁻¹⁷ Because appropriate patient selection determines which patients can undergo limited neck surgical exploration for parathyroidectomy, we reviewed our experience to determine the utility of IOPTH monitoring for patients with PHPT as a result of DA disease.

METHODS

The study was a retrospective chart review of 552 consecutive patients who underwent intervention for PHPT at Johns Hopkins Medical Institutions, Baltimore, Maryland, between June 2002 and May 2007. Patients were excluded if they had at least 1 of the following conditions: familial hyperparathyroidism, any of the multiple endocrine neoplasia syndromes, or recurrence or persistence of hyperparathyroidism after previous parathyroid operations. The study included 47 patients with PHPT who had DAs identified during first-time parathyroid exploration. The following data were collected: demographics, preoperative serum calcium and iPTH levels, IOPTH assay results, surgical findings, histopathologic results, and postoperative serum calcium and iPTH levels.

The diagnosis of a DA was based on the surgeon's clinical impression that the glands were enlarged, especially by weight and by an appropriate decrease in IOPTH levels after removal of both abnormal glands. The IOPTH levels were measured in every case. All 47 patients were approached with targeted parathyroidectomy for presumed single-gland disease. However, in cases in which IOPTH levels did not decrease to the normal range, the surgeon continued to look for a second adenoma. If a second adenoma was found and the IOPTH level decreased to normal, the search for additional glands to rule out hyperplasia ended at that point. The IOPTH assay and its influence on surgical outcome were examined.

RESULTS

A total of 47 patients (8.5%) were found to have DAs; 457 patients (82.7%) had single adenomas; and 48 patients (8.6%) had multiglandular disease (in more than 2 glands). The mean (SD) age of the patients with DAs was 58 (14) years, and 26 patients (55%) were female. There was no racial disparity in the incidence of DA disease; however, DA was proportionately more common in men than single-gland disease (**Table**).

The mean (SD) preoperative iPTH level was 129 (57) pg/mL (to convert to nanograms per liter, multiply by 1), and the mean (SD) preoperative serum calcium level was 11.0 (0.6) mg/dL (to convert to millimoles per liter, multiply by 0.25). After the first adenoma excision, the mean (SD) IOPTH value was 130 (88) pg/mL after 10 minutes (reference range, 44-500 pg/mL). The mean percentage of decrease in IOPTH levels after the first adenoma excision was 43.6%. The IOPTH levels decreased by an average of 79.7% (11.4%) from baseline after removal of both abnormal parathyroid glands (**Figure**), which was comparable to 78.8% (10.7%) in patients with a single adenoma ($P=.65$) (Table). The second adenoma was ipsilateral in 17 patients (36%) and contralateral in 27 patients (64%).

The mean postoperative iPTH level at 6 months was 46 (26) pg/mL. Of the 47 patients, 46 (98%) remained normocalcemic after surgery. The 1 patient who had persistent hypercalcemia elected to be treated with medication after surgery.

Table. Comparison Between Single- and Double-Adenoma Groups

Variable	Single Adenoma (n=457)	Double Adenoma (n=47)	P Value
Age, mean (SD), y	60 (13)	58 (14)	.40
Female sex, %	75	56	.01
Race, %			
Black	19	13	
White	78	87	.18
Other	3	0	
Alkaline phosphatase, U/L	99 (40)	92 (27)	.37
Calcium, mg/dL			
Before surgery	11.4 (3.9)	11.0 (0.6)	.54
1 Week after surgery	9.8 (2.6)	9.4 (1.0)	.41
6 Months after surgery	9.5 (0.5)	9.8 (0.5)	.16
PTH, pg/mL			
Before surgery	146 (115)	129 (57)	.35
% Reduction in intraoperative PTH values at end of surgery	79 (11)	80 (11)	.65
1 Week after surgery	51 (36)	38 (34)	.04
6 Months after surgery	51 (40)	46 (26)	.65

Abbreviation: PTH, parathyroid hormone.

SI conversion factors: To convert alkaline phosphatase to microkatal per liter, multiply by 0.0167; to convert calcium to millimoles per liter, multiply by 0.25; to convert PTH to nanograms per liter, multiply by 1.

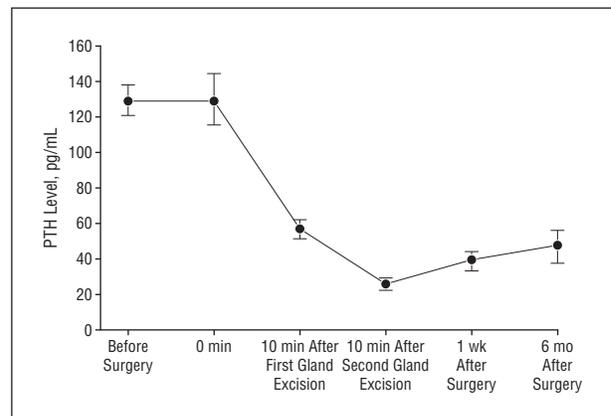


Figure. Mean intraoperative parathyroid hormone (PTH) values for 47 patients (to convert PTH values to nanograms per liter, multiply by 1). Baseline values were obtained before neck incision. Postoperative values were obtained 0 and 10 minutes after the first adenoma excision and 10 minutes after excision of the second adenoma. Postoperative values were obtained 1 week and 6 months after surgery. Error bars indicate SEM.

COMMENT

Some investigators have suggested that DAs do not exist and instead represent cases of asymmetrical primary hyperplasia.⁸ In contrast, in many recent series, DAs have been reported to occur in 2% to 15% of patients with PHPT.²⁻⁶ Accurate identification of DAs depends on the ability of the surgeon to distinguish adenomatous from hyperplastic glands.^{8,18} The adenoma was described as a neoplastic lesion that was solitary and surrounded by a rim of normal-appearing parathyroid tissue. In contrast, hyperplasia was defined as a diffuse enlargement of all glands with a rather monotonous uniformity.³ Histopathologic differentiation of adenoma from hyperplasia is difficult at best.

Attempts have been made to distinguish patients with DAs on clinical grounds. In some studies,^{4,6} patients with DAs were older and had significantly higher iPTH levels than those with a solitary adenoma or 4-gland hyperplasia. Our study showed that the patients with DA disease were of a similar age and had similar preoperative iPTH, serum calcium, and alkaline phosphatase levels in comparison to the patients with single-adenoma disease (Table).

The inability to distinguish adenoma from hyperplasia on histologic grounds has resulted in different recommendations about the appropriate surgical management of PHPT. The pathologists at our institution agree that histopathologic differentiation of adenoma from hyperplasia is difficult. In our opinion, the diagnosis of an adenoma is based on the surgeon's clinical impression that the gland is enlarged.

The use of IOPTH measurement in parathyroid surgery was introduced, and parameters for its use as an indicator of adequate parathyroidectomy are replete in the medical literature.¹⁹ An appropriate decrease in the IOPTH level suggests that hyperfunctioning parathyroid tissue has been removed, and it does predict postoperative normocalcemia in patients with a single adenoma. For most authors, the rapid IOPTH assay is an effective tool in determining the success of parathyroidectomy in patients with primary and recurrent hyperparathyroidism.¹⁹ It can be used to help achieve minimally invasive parathyroidectomy explorations or to guide surgical decision making in more complex cases. It is worth noting that nonsynchronous DAs or suppressed DAs may represent a pitfall in minimally invasive parathyroidectomy and may be responsible for the late recurrence of hyperparathyroidism.^{20,21}

In our series, of the 47 patients, 46 (98%) remained normocalcemic after surgery and remained so for at least 6 months. Only 1 patient was still hypercalcemic after surgery and was treated with medication. Therefore, we believe that IOPTH monitoring is a very useful tool to predict a durable biochemical resolution of hyperparathyroidism in patients with DAs.

In conclusion, the decrease in IOPTH levels and the maintenance of normocalcemia after surgery confirm previous reports that DAs do exist and are not simply missed cases of 4-gland hyperplasia. Intraoperative PTH monitoring accurately predicted the success of parathyroidectomy in 98% of patients with DAs. A reduction in the IOPTH levels by more than 50% and into the normal range can be used as a highly accurate predictor of cure in patients with DAs. Therefore, IOPTH monitoring is a very useful tool in patients with PHPT and DA disease.

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Correspondence: Ralph P. Tufano, MD, Department of Otolaryngology–Head and Neck Surgery, Division of Head and Neck Cancer Surgery, Johns Hopkins School of Medicine, Baltimore, MD 21287-0910 (rtufano@jhmi.edu).

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interpretation of data: Islam and Tufano. *Drafting of the manuscript:* Kandil and Alabbas. *Critical revision of the manuscript for important intellectual content:* Bansal, Islam, Tufano, and Tufano. *Statistical analysis:* Islam. *Administrative, technical, and material support:* Bansal. *Study supervision:* Tufano and Tufano.

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