

# Validation study of intraoperative fine-needle aspiration of parathyroid tissue with measurement of parathyroid hormone levels using the rapid intraoperative assay

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**Background:** Surgical treatment of hyperparathyroidism relies on the ability to accurately identify parathyroid tissue. The use of intraoperative fine-needle aspiration (FNA) with measurement of intact parathyroid hormone level (iPTH-FNA) has been suggested as a useful adjunct and is evaluated in this pilot study.

**Methods:** An institutional review board–approved retrospective review was performed on patients undergoing parathyroid exploration for primary hyperparathyroidism who also underwent selective FNA at the end of the procedure. FNA was performed on excised parathyroid tissue, ipsilateral thyroid tissue, and muscle.

**Results:** Ten patients underwent FNA. Mean iPTH-FNA values were 1559.6 pg/mL (range, 675–1775) for parathyroid, 51.4 pg/mL (range, 10–248) for thyroid, and 34.1 pg/mL (range, 14–128) for muscle. All iPTH-FNA assay results were significantly higher for parathyroid tissue than for either thyroid tissue ( $P < 0.05$ ) or muscle ( $P < 0.05$ ). There were no significant iPTH-FNA assay differences between thyroid and muscle ( $P = 0.09$ ).

**Conclusions:** Intraoperative FNA of parathyroid tissue with the rapid iPTH assay can correctly identify parathyroid tissue. It may prove to be a useful surgical adjunct in the treatment of hyperparathyroidism.

Management of hyperparathyroidism has been clarified by a National Institutes of Health conference: surgical removal is recommended in patients with serum calcium  $>10.5$  mg/dL without symptoms or  $>10.0$  with symptoms (1). The surgical treatment of hyperparathyroidism has evolved over the past 5 years. The development of the technetium Tc 99m sestamibi scan has allowed for a minimally invasive approach with unilateral neck exploration and removal of the enlarged gland. The development of the rapid intraoperative intact parathyroid hormone (iPTH) assay has allowed for confirmation of clinical cure based on an appropriate drop in the iPTH level following excision of the adenoma. These two modalities have been widely accepted.

Fortunately, a solitary adenoma is present in approximately 75% of operative cases, allowing for a straightforward surgical procedure requiring  $<1$  hour and generally allowing for hospital discharge in  $<23$  hours. However, there remains an approximate 25% chance for a second adenoma, an intrathyroidal adenoma, four-gland hyperplasia, or an adenoma that is simply difficult to find.

Successful surgical treatment of hyperparathyroidism depends on the surgeon's ability to identify parathyroid tissue in the operative field. Normal and abnormal parathyroid tissue may closely resemble adjacent nodular thyroid tissue, fat, or lymph nodes and may be located in ectopic locations. Although most patients have four parathyroid glands, some have three or five glands. On occasion, a parathyroid gland is located within the thyroid gland, and successful identification requires a thyroid lobectomy. Identification of parathyroid tissue is particularly challenging in the operative setting due to scarring. Confirmation of parathyroid tissue is usually obtained based on pathologic frozen section analysis. This may require partial excision of a parathyroid gland, which may damage its blood supply. Pathologic analysis may add

significant time and cost to a procedure if multiple samples are required.

Several groups have described preoperative fine-needle aspiration (FNA) of suspicious parathyroid tissue with iPTH (2–5). The general consensus is that a markedly elevated iPTH level by FNA is diagnostic of parathyroid tissue and is a simple and efficient tool to use preoperatively. Perrier et al recently reported the use of the rapid iPTH assay during intraoperative FNA (6). In the study's 65 patients, this technique was found to be 100% sensitive and 100% specific for the identification of parathyroid tissue. This application is made very convenient for the surgeon, as the rapid intraoperative iPTH assay is routinely employed during parathyroid surgery. This article evaluates our initial clinical experience using the rapid iPTH assay with intraoperative FNA of parathyroid tissue (iPTH-FNA).

## METHODS

An institutional review board–approved retrospective review was performed on patients undergoing parathyroid exploration for primary hyperparathyroidism who also underwent selective FNA at the end of the procedure. All patients were treated by three surgeons between August 2003 and January 2005. When primary hyperparathyroidism is suspected, general evaluation of patients includes serum calcium level, serum intact PTH level, and sestamibi scan. All patients also underwent cervical ultrasound at the surgeon's office during their preoperative visit.

The surgical procedure involved unilateral neck exploration based on the preoperative imaging. The use of the iPTH assay is described elsewhere (7, 8). In general, intraoperative blood

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samples are drawn peripherally before skin incision, before excision of the abnormal parathyroid tissue, and at 5 and 10 minutes after excision. Surgical excision of abnormal parathyroid tissue is considered complete when the intraoperative PTH level decreases by at least 50% of the highest intraoperative value before excision. The Quick-IntraOperative Intact PTH Assay Kit (Nichols Institute Diagnostics, San Clemente, CA) has 10 assays, which are charged as a single unit, regardless of the number of assays performed. Unused assays are discarded. Normally, three to five levels are drawn in a routine case.

In selected cases when the iPTH level decreased appropriately, the remaining unused samples from the rapid iPTH kit were used to evaluate FNA specimens. FNA was performed with a 3- or 5-mL syringe containing 2 mL of saline. Two to three passes were made through the tissue of interest with a 25-gauge needle while applying suction via the syringe. Saline (1 mL) was aspirated through the needle into the syringe. This sample was sent to the laboratory for analysis. FNA was performed on the excised parathyroid adenoma *ex vivo*, on the ipsilateral thyroid lobe, and on adjacent strap muscle or sternocleidomastoid muscle. Results were made available to the surgeon at the conclusion of the case.

## RESULTS

Ten patients were treated for primary hyperparathyroidism and underwent intraoperative FNA of one focus of parathyroid tissue. All surgeries were considered successful based on appropriate decrease of iPTH serum levels. Hypercalcemia was resolved in all patients at a median follow-up of 6 months (range, 2–16 months).

There were no complications related to FNA. FNA results are shown in the *Table*. All parathyroid tissue that underwent FNA was confirmed to be parathyroid tissue pathologically. Eight parathyroid glands that were aspirated were adenomas, one was hyperplastic, and one was grossly enlarged but histologically normal. Mean iPTH-FNA values were 1559.6 pg/mL (range, 675–1775) for parathyroid, 51.4 pg/mL (range, 10–248) for thyroid, and 34.1 pg/mL (range, 14–128) for muscle. Most iPTH-FNA results from parathyroid tissue were greater than the highest numeric value possible based on the assay. iPTH-FNA results of a solitary normal gland and of a hyperplastic gland were less dramatically elevated. All iPTH-FNA assay results were significantly higher for parathyroid tissue than for either thyroid tissue ( $P < 0.05$ ) or muscle ( $P < 0.05$ ). There were no significant iPTH-FNA assay differences between thyroid and muscle ( $P = 0.09$ ).

## DISCUSSION

Minimally invasive parathyroid surgery is possible with a preoperative sestamibi scan that localizes to an apparent solitary parathyroid adenoma. The intraoperative assessment for reduction of serum iPTH levels is a complementary tool used by many surgeons to confirm successful excision of parathyroid tissue. The equipment for the assay requires an initial capital expenditure and personnel commitment during surgery. Each individual assay requires an enzyme-linked immunosorbent assay type of kit with reagents and adsorbent beads, which are read in a photometer. The cost of the kit is largely related to the reagents (\$800/kit). Of the 10 assays per kit, four are used at baseline, preexcision,

**Table. Intraoperative intact parathyroid hormone assay results on fine-needle aspirates and pathologic diagnosis of parathyroid tissue**

Patient number	Pathologic diagnosis of parathyroid tissue	iPTH-FNA value (pg/mL)		
		Parathyroid	Thyroid	Muscle
1	Adenoma	>1775*	26	24
2	Adenoma	>1775	10	17
3	Adenoma	>1775	54	20
4	Adenoma	>1775	16	18
5	Adenoma	>1775	248	128
6	Adenoma	>1775	74	68
7	Adenoma	>1775	38	19
8	Adenoma	1700	15	15
9	Normal gland	675	17	18
10	Hyperplastic	796	16	14

iPTH-FNA indicates use of the rapid intraoperative intact parathyroid hormone assay with intraoperative fine-needle aspiration of parathyroid tissue.

\*The upper limit of the iPTH assay is 1775.

5 minutes postexcision, and 10 minutes postexcision. Six other assays remain for testing of parathyroid tissue or serum levels.

The use of FNA of parathyroid tissue is potentially beneficial in the intraoperative setting. The current study demonstrates that the results are reproducible and quite uniform. In this series, all FNA specimens were taken of already excised parathyroid glands. If applied to glands *in situ*, FNA is potentially less likely to cause significant damage to a parathyroid gland as opposed to an incisional biopsy with cauterization of the cut surface of the gland, which is the current method of confirming parathyroid tissue. Certainly, any manipulation or aspiration of parathyroid glands has the potential to cause gland injury. Minimizing trauma to remaining parathyroid glands is of paramount importance in avoiding transient or permanent hypoparathyroidism.

In this series and others, iPTH-FNA values of >600 pg/mL are always indicative of parathyroid tissue (6). The iPTH assay has an upper limit to its numeric result. On serum samples, this value is not approached. The most common value in this series and in that from the University of California at San Francisco was a value greater than the upper limit of detection of the assay (6). Diluting the sample 1:10 in the University of California study did not significantly decrease the assay value. Based on these retrospective reviews, a markedly elevated iPTH-FNA result is confirmatory of parathyroid tissue.

In two patients, intraoperative FNA was obtained from hyperplastic and normal parathyroid tissue, which resulted in values markedly lower than those from adenomatous tissue. Conclusions regarding the ability to differentiate between normal, hyperplastic, and adenomatous tissue cannot be drawn given the small sample size. Kiblut et al studied iPTH-FNA in normal and adenomatous parathyroid tissue and found no significant difference in values between the two (9). Thus, that study suggested that FNA using the rapid iPTH assay cannot be used to differentiate parathyroid adenoma from hyperplasia or normal parathyroid tissue. Clinical evaluation, pathologic examination,

and the rapid iPTH assay results are still the methods of choice for differentiating these tissues.

There have been no reports of iPTH-FNA techniques in parathyroid carcinoma. In this rare condition, the diagnosis is made based on clinical findings at the time of surgery and characteristic histologic findings (10). Thus, the utility of iPTH-FNA in differentiating benign from malignant parathyroid disease is as yet unknown.

FNA takes less than 1 minute to perform, with results available in 5 to 10 minutes. The patient is charged a flat fee of roughly \$800 for the rapid iPTH kit and assays, regardless of the number of assays used. A new kit is opened for each patient. Judicious use of iPTH-FNA, keeping in mind the number of assays needed for serum rapid iPTH levels, may provide the surgeon with useful information.

The potential cost savings includes avoidance of a pathologic frozen section for confirmation of a solitary parathyroid adenoma, which is excised in most cases. The global charge for a frozen section is approximately \$300 at Baylor University Medical Center (personal communication). In almost 25% of cases, additional searching for second adenomas, four-gland hyperplasia, or intrathyroidal adenomas may require additional frozen sections of various fatty tissue, lymph nodes, thyroid tissue, and normal parathyroid tissue. In these cases, FNA of suspected parathyroid tissue can be performed for confirmation of parathyroid tissue with incremental cost savings for each specimen.

In conclusion, intraoperative FNA of parathyroid tissue with the rapid iPTH assay can correctly identify parathyroid tissue. It is a potential cost-effective use of unused assays in the rapid iPTH kit.

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