A New Approach to Parathyroidectomy

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Objective

To decrease the operative time for parathyroidectomy in patients with hypercalcemic (primary) hyperparathyroid disease, a combination of preoperative localization of a parathyroid tumor with an effective nuclear scan (scintigram) and intraoperative monitoring of parathyroid hormone (quick parathyroid hormone measurement) to ensure excision of all hyperfunctioning tissue was studied.

Summary Background Data

For many years, persistent hypercalcemia after parathyroidectomy (3% to 10%) has been constant and is usually due to the surgeon’s failure to remove all hyperfunctioning glands. A marked decrease in parathormone level after excision of a single large gland predicts operative success and a return to normal calcium levels. Conversely, persistent high levels of parathyroid hormone indicate excess secretion by another gland(s) and the need for further exploration. Recently Tc-99m-sestamibi (MIBI) scintigraphy was shown to be more effective in localizing parathyroid tumors than previous methods. A combination of both techniques could be useful to the surgeon if they improve the operative success rate and are cost-effective.

Methods

Parathyroidectomy was performed on 18 patients with primary hyperparathyroid disease, with tumors localized by MIBI scintigrams. When excision of the identified parathyroid gland was accomplished, the operation was terminated and quick parathyroid hormone was measured to confirm that all hyperfunctioning tissue was removed.

Results

Sixteen patients with positive results of scintigram had successful parathyroidectomies confirmed by quick parathyroid hormone measurement with a cervical approach. Two patients with mediastinal tumors localized by MIBI scintigraphy could not be resected using this approach. One false-positive/false-negative scintigram was obtained. Compared with patients having parathyroidectomy without localization and hormone monitoring, the average operative time was shortened from 90 to 36 minutes.

Conclusions

Localization and successful excision of parathyroid tumors with confirmation that no other hyperfunctioning glands were present by quick parathyroid hormone monitoring can predict a return to normal calcium levels and a decrease in operative time in parathyroidectomy.
Patients with hypercalcemic (primary) hyperparathyroid disease have been treated successfully using parathyroidectomy, with reported cure rates of 90% to 96%.\(^1\) However, persisting postoperative hypercalcemia in 3% to 10% of patients has been a consistent finding in large series of patients for many years.\(^2\)-\(^4\) Sometimes these failures are due to a misdiagnosis or an aberrant location of the tumor (mediastinum). More often, operation is unsuccessful because the surgeon fails to identify and remove all hyperfunctioning parathyroid glands. Because more than one gland is effected in 7% to 26% of patients, many surgeons remove the obviously enlarged gland and thoroughly explore both sides of the neck.\(^1\),\(^2\),\(^5\) Further removal of parathyroid tissue is then based on the size and appearance of the remaining glands and the surgeon’s experience.

Tc-99m-sestamibi scintigraphy has been shown to be an effective method for localizing parathyroid tumors.\(^6\)-\(^8\) With accurate localization using this technique, a quick and direct surgical procedure can be performed that identifies and excises the parathyroid tumors. If the surgeon could be sure that other hyperfunctioning glands were not present, further exploration would not be needed and the operation could be terminated rapidly. Intraoperative measurement of intact parathyroid hormone (PTH) provides the surgeon with a quantitative test that predicts the postoperative serum calcium level and can justify early closure or further exploration for hyperfunctioning parathyroid tissue.\(^9\),\(^10\) A combination of these two techniques, if it improves the success rate of parathyroidectomy, shortens the time of surgery, or both, and is cost-effective, suggests a new surgical approach in patients with primary hyperparathyroid disease.

**METHODS**

Eighteen consecutive patients with established hypercalcemic (primary) hyperparathyroid disease had cervical explorations for treatment of the disease. All patients had elevated preoperative serum calcium levels averaging 12.3 mg/dL (range, 10.2 to 12.8 mg/dL) and intact PTH levels above the normal range for the assays used. Two patients had previous neck explorations for thyroid or parathyroid disease. All patients had normal renal function, except for one (serum creatinine, 2.1 mg/dL) with a late recurrence 10 years after his first parathyroidectomy.

As part of the preoperative evaluation, a Tc-99m-sestamibi (DuPont Merck Pharmaceutical, Billerica, MA) parathyroid scintigram was performed. The usual dose was 20 to 25 mCi injected intravenously, followed immediately by planar (Picker Corp., Northford, CT) and tomographic reprojection (single photon emission computed tomography) (Trionix Research Laboratory, Twinsburg, OH) scintigrams. Subsequently patients were examined again approximately 2 hours after injection. The delay between the early and late scintigrams allowed the preferential uptake by the parathyroid tumor to be visualized after dissipation of most of the isotope from surrounding tissues such as the thyroid gland.\(^11\) All patients had positive results of scintigrams, with tumor images localized either in the right or left neck or in the mediastinum. Interpretation of planar images was performed as usual, whereas the tomographic images were reviewed on a computer monitor allowing a three-dimensional reprojection rotating image of the neck and upper chest, which helped define the location of the parathyroid tumor in depth and position relative to the thyroid gland and other anatomic landmarks.

The surgical procedure in each case was based on the location of the parathyroid tumor as identified by the nuclear scintigram. After general endotracheal anesthesia, a low cervical incision was made, skin flaps were raised, and the strap muscles were opened in the midline. Exploration was directed to the site identified before operation and any grossly abnormal-appearing parathyroid gland was removed and sent to the pathology laboratory for histologic confirmation. At this point, no further dissection was done and the wound was closed. Five minutes after excision of tissue, a peripheral venous blood sample was obtained and processed for quick parathyroid hormone (QPTH) determination. Light anesthesia was maintained until the results of the QPTH assay were available. If the hormone level decreased substantially in the 5-minute postexcision sample (as defined below), the patient was awakened and returned to the recovery room. On the other hand, if there was little or no decrease in the PTH level, the closed wound was opened and exploration continued for any remaining hyperfunctioning glands.

Measurement of the intact PTH, which has a half-life of 3 to 4 minutes, was done by an intraoperative immunoradiometric assay (IRMA) in nine patients. As previously described,\(^9\),\(^10\) perioperative 6-mL blood samples were taken from a peripheral vein at the following times: after induction of anesthesia but before any incision; after dissection and just before tumor excision; and 5 minutes, 10 minutes, and 20 minutes after parathyroid excision. Each sample was divided into two tubes: one for

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Presented at the 105th Annual Scientific Session of the Southern Surgical Association, December 5-8, 1993.

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Accepted for publication January 11, 1994.
later PTH determination by a standard 24-hour IRMA (INCASTAR Corp., Stillwater, MN or Nichols Institute Diagnostics, San Juan Capistrano, CA) and the other shaken in ethylenediamine tetraacetic acid for anticoagulation and use in the QPTH assay.

Quick PTH was measured with a modification of a commercially available two-site antibody immunoradiometric assay (INCASTAR Corp.) using a small portable gamma counter (MGM Electronics, Hamden, CT) in or just outside the operating room; turnaround time of the assay is 12 minutes. A decrease in the PTH level of 50% or more in the 5-minute postexcision sample compared with the highest preoperative or pre-excision sample was used to predict a return to normal calcium levels after operation. Using this assay in patients with primary hyperparathyroid disease, we previously reported that a 50% decrease in the 10-minute postexcision sample has a sensitivity rate of 96% and overall accuracy rate of 97%.10

More recently, we used a modified immunochemical luminescence assay (ICMA) for intraoperative monitoring of intact PTH (Nichols Institute Diagnostics). This two-site antibody assay is similar to the IRMA but uses acridinium ester as a label instead of radioisotopes.12,13 Quick PTH is measured in the operating room using a small portable luminometer (MGM Electronics, Hamden, CT) with a turnaround time of less than 15 minutes. Modifications of the standard 2-hour ICMA include using ethylenediamine tetraacetic acid plasma after ultracentrifugation (Brinkmann Instrument Co., Westburg, NY) for 30 seconds, shaking at 800 rpm, heating to 45°C with a heat-controlled shaker (IKA-Works, Staufen, Germany) for 10 minutes, washing with buffered saline, and counting duplicate tubes for 2 seconds each in the luminometer. The intact PTH level in each sample is measured in relative light units and expressed by computer analysis in picograms per deciliter based on a precalculated standard curve. The percentage decrease is measured from the highest preoperative or pre-excision PTH level, as described for the IRMA.9 Again a decrease of more than 50% in the 5-minute postexcision sample was considered to be predictive of a postoperative return to normal calcium levels. This assay was shown to be more sensitive than the IRMA and was used for intraoperative monitoring in the last seven patients reported in this series.

Using the approach described, confirmation that all hyperfunctioning parathyroid tissue has been removed is available between 17 and 20 minutes after excision of the parathyroid adenoma, often before the histologic report on the frozen section is available.

RESULTS

Figure 1 shows a representative scintigram in 1 of the 18 patients operated on in this series; a parathyroid tu-

mor is clearly identified in the right neck, with proximity to the thyroid gland when the early and late planar images are compared. In Figure 2, selected views of the re-projection single photon emission computed tomographic study show the three-dimensional computer rotating image in the same patient, which places the parathyroid tumor just below and dorsal to the inferior pole of the right lobe of the thyroid gland. This type of localization helps the surgeon enormously to shorten the operative procedure. In the 16 patients with tumors localized in the neck, all had successful parathyroidectomies resulting in normal calcium levels after operation. In one patient, the scintigram provided both false-positive and false-negative information, suggesting a tumor laterally and superior to the thyroid lobe and missing its true inferior position. At operation in this patient, a large parathyroid tumor was found inferior to the thyroid in juxtaposition to the trachea, removal of which was followed by a 50% decrease in QPTH 5 minutes later; a thorough search of the area suspected on the basis of the scintigram, including biopsy of a normal-sized superior
Parathyroidectomy, when performed by experienced surgeons, is very successful in patients with hypercalcemic (primary) hyperparathyroid disease, with cure rates of 90% to 96%. On the other hand, the failure rate for this operation has not changed much during the last two decades. In our series of patients, persistent hypercalcemia after parathyroidectomy was 10% in 1972 and 7% in 1991.

In the last 2 years, 3 of 42 patients (7%) remained hypercalcemic after their first parathyroidectomy. Our experience with MIBI parathyroid scintigraphy suggests that these three patients could have been spared failed operations. Two patients had positive results of scintigram with localized tumors in the mediastinum. Although most parathyroid tumors in the anterior mediastinum can be removed through a cervical incision, we have subsequently learned that when the distance between the thyroid and the parathyroid tumor is as great as shown in Figure 3, further localizing studies are needed to establish the best operative approach, either by thoracotomy or median sternotomy. We would not recommend a cervical approach under these circumstances. The third unsuccessful parathyroidectomy was done on a patient in the surgical intensive care unit with severe pancreatitis, hypercalcemia, and a contaminated tracheostomy wound who was dependent on a ventilator. Ultrasonography suggested a parathyroid mass in the right neck, and exploration was done through a right lateral incision to isolate the tracheostomy. No tumor was found and the operation was aborted because of the patient’s unstable condition. Two days later, a large (2 cm) parathyroid adenoma behind the left lobe of the thyroid was removed on repeated exploration. Today, a tumor of this size would probably be localized correctly using an MIBI scintigram, thus indicating the appropriate operative approach to the left-sided lesion. Increased experience with and availability of MIBI scintigraphy probably would have prevented these three unsuccessful parathyroidectomies, thereby enhancing our success rate.

Any technical modality offered to enhance surgical practice must be justified by its ability to increase the suc-
cess of the operation and its cost-effectiveness. The cost of each MIBI scintigram is approximately $600; if applied to all 42 patients ($25,200) to improve the success rate by saving three repeated operations ($24,000), preoperative MIBI scintigraphy in all patients is an expense that is not easily justified. Our approach of combining this effective but costly localizing technique with intraoperative PTH monitoring is designed to ensure not only a successful operation but one that is completed in the shortest possible time, thereby reducing operating room and anesthesia costs. Extended operative time usually results from dissection and exploration to identify the remaining parathyroid glands. The results reported here using the QPTH assay as a “biochemical frozen section” make routine examination of the remaining glands unnecessary, thereby shortening the operative time in most cases. In our medical center, operating room costs increase by approximately $1,000 for each 30 minutes after the first hour. In the patients described here, in whom these techniques were applied, average operative time was decreased to 36 minutes from the 90 minutes required in other patients not subject to these procedures. Projection of an average saving of $1000 per patient in operating room charges suggests a strong basis for cost-effectiveness.

Parathyroid hormone monitoring may be unnecessary when the patient has a positive result of MIBI scintigram. In the small series of patients described here, one scintigram was incorrectly interpreted and one well-localized, hyperfunctioning gland was overlooked. In these two patients, the QPTH assay correctly identified the problems, thus helping to ensure successful parathyroidectomy. The sensitivity and specificity rates of MIBI parathyroid scintigram and its ability to localize all hyperfunctioning glands have not been determined. Therefore, without intraoperative PTH monitoring, it would still be necessary to examine all four parathyroid glands even when a single hyperfunctioning gland is seen on the scintigram. The need for this is clear because 14% of 414 our patients with primary hyperparathyroid disease had more than one hyperfunctioning gland.

Although the immunoradiometric QPTH assay has been used successfully for intraoperative monitoring in our medical center for the past 3 years, this method has two disadvantages. The radioisotopic label has a short half-life, which limits the time of utility for each assay kit, and the test has a false-negative rate of 15%. The modified two-antibody ICMA appears to be more sensitive and stable than the IRMA. The ICMA kit shelf-life of 6 months makes it more practical for intraoperative use. Clinical validation of this assay is limited by the small number of patients in our series, but a correlation

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<th>Patient No.</th>
<th>QPTH Preoperative or Post-Excision (pg/dL)</th>
<th>Decrease (%)</th>
<th>24-Hour PTH IRMA</th>
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* Delayed, 10 minute post-excision sample.
of the ICMA QPTH results and the 24-hour IRMA control appears satisfactory. Kao and associates,\textsuperscript{15} using a similar chemiluminescence method to measure intact PTH, reported very good correlation of their intraoperative assay with a 15-minute incubation time and their standard 18-hour assay. The cost of intraoperative PTH monitoring has not been determined at this stage of its development.

The combination of MIBI parathyroid scintigram for accurate localization of tumors and rapid intraoperative determination of possible hypersecretion by the remaining glands after tumor excision is a useful surgical adjunct. Using a combination of these two new techniques, operating time has decreased, which suggests a cost-effective approach to improving the success rate of parathyroidectomy.

Acknowledgments

The authors thank Tammy R. Kopelman, M.D., Lawrence M. Fishman, M.D., Michael Georgiou, M.S., Joseph N. Foss, M.D., and Luke Yeung, M.D., for their assistance in this study.

References


Discussion

Dr. John P. Wei (Augusta, Georgia): Today, Dr. Irvin has attempted in this circumstance to join two new emerging technologies in the hopes of improving the success of initial parathyroidectomies for patients with primary hyperparathyroidism. As with any emerging new technique, an experience to define the limitations and refinement of the techniques are necessary, and delineation of areas of potential failure is necessary prior to wide dissemination and common use of these techniques. In the old days, when a woman was first found to be with child, people had to wait until the rabbit died before they knew she was pregnant. Nowadays, all you have to do is look in the bottom of the test tube and see whether it turns blue or not. Now until parathyroid localization can be developed to the point that it can be done in a rapid time and in such a manner that everyone can apply it with a 100% success rate, then by and large it should still be considered investigational. First, the nature of the parathyroid embryological development and potential mediastinal descent will always contribute to a small percentage of initial parathyroid surgical failure. As in Dr. Irvin’s case, two out of his 18 patients in this series were surgical failures because of this anatomic constraint. I ask Dr. Irvin if, given successful preoperative localization, he would proceed to mediastinotomy for resection if he has sufficient confidence in his techniques that he would open the sternum after a failed surgical operation. Second, the limits of resolution of any radionuclide study will always be dependent upon the atomic physics of that isotope. By and large, most of the currently existing technologies have fallen by the roadside. Technetium-thallium has been deemed a failure by John Doppman. A year and a half ago in Miami, he basically stated that, as they quoted, “All you need is a good surgeon to find the parathyroid adenoma.” The limitations of the test have to be considered in the utilization of that test. The physical relationships to the thyroid gland and specific pathologic anomalies of a thyroid may give rise to difficulties in interpretation of that test. As Dr. McGarity showed, it is possible to have false-positives because of thyroid pathology. And as Dr. Irvin himself noted, he had two cases in which he had difficulty with interpretation of his scans. Third, the ultimate success rate of the operation is dependent upon a surgeon and his capability to recognize and identify intraoperative...