Objective: To evaluate the utility of a rapid intraoperative parathyroid hormone (PTH) immunoradiometric assay in the surgical management of parathyroid disease, particularly with reference to limiting extent of cervical exploration.

Design: Nonrandomized prospective study.

Setting: Academic tertiary care center.

Patients: Forty-three consecutive patients undergoing parathyroid exploration for adenoma or hyperplasia had rapid PTH assays performed from blood drawn at induction and 7 minutes after resection of all hyperfunctioning parathyroid tissue.

Outcome Measures: Excision of all hyperfunctioning parathyroid tissue as assessed by bilateral neck exploration, postoperative normalization of serum calcium and PTH levels, and resolution of clinical symptoms.

Results: The intraoperative rapid PTH assay accurately reflected whether all hyperfunctioning parathyroid tissue was excised in every patient. In 41 patients, all hyperfunctioning parathyroid tissue was resected at the time of surgery and confirmed by a corresponding decrease in the intraoperative postexcision rapid PTH determination as well as by subsequent normalization of postoperative serum calcium and PTH levels and resolution of clinical symptoms. In 2 patients, the postexcision rapid PTH assay determination was not consistent with removal of all hyperfunctioning parathyroid disease and both patients demonstrated persistent hyperparathyroidism postoperatively.

Conclusions: The intraoperative rapid PTH assay may be of significant benefit in permitting directed unilateral parathyroid explorations for adenoma when combined with preoperative localization with a technetium-99m sestamibi scan. Additionally, the rapid PTH assay has proved to be of benefit in confirming excision of all hyperfunctioning parathyroid tissue in patients with multiple gland hyperplasia, particularly those who may harbor ectopic parathyroid tissue.


The extent of surgical exploration required for patients with primary hyperparathyroidism as a result of parathyroid adenoma has not been clearly defined. Several authors advocate unilateral neck exploration in patients with preoperatively localized parathyroid adenomas, citing reductions in operative time and morbidity as potential benefits.1-3 Others argue in favor of bilateral cervical exploration in all patients with primary hyperparathyroidism in order to avoid missing multiple adenomas or unrecognized hyperplasia.4-6

The recent development of a rapid parathyroid hormone (PTH) immunoradiometric assay now allows intraoperative determination of serum PTH levels and thus may be used to confirm resection of all hyperfunctioning parathyroid tissue. Nussbaum et al7 and Irvin et al8,9 recently demonstrated that the intraoperative use of a rapid PTH assay can serve as a valuable adjunct in limiting the extent of neck exploration for primary hyperparathyroidism secondary to adenoma.

The intent of this discussion is to describe our experience with the use of a rapid intraoperative PTH immunoradiometric assay in patients undergoing cervical exploration for both parathyroid adenoma and multiple gland hyperplasia. In particular, the efficacy of this procedure for directed parathyroid exploration in preoperatively localized parathyroid adenoma is discussed.

Results

Of the 43 patients evaluated in this study, parathyroid adenoma was histologically...
PATIENTS AND METHODS

A prospective evaluation was conducted on 43 consecutive patients undergoing exploration for adenoma or hyperplasia at Geisinger Medical Center, Danville, Pa, between January 1, 1995, and December 31, 1996. All patients were evaluated preoperatively by both the Department of Otolaryngology–Head and Neck Surgery and the Department of Endocrinology. Informed consent for bilateral neck exploration and intraoperative rapid PTH immunoradiometric assay sampling was obtained for all patients. This study was not submitted for review by our institutional research review board. The diagnosis of hyperparathyroidism was determined biochemically based on serum values of calcium and PTH and urinary calcium levels as well as on clinical symptomatology. All patients with primary hyperparathyroidism who were suspected of having a parathyroid adenoma underwent preoperative localization with a technetium-99m sestamibi scan. A rapid PTH immunoradiometric assay was developed in the Department of Laboratory Medicine at Geisinger Medical Center through a simple, previously described modification of an intact PTH overnight assay method (Nichols Institute Diagnostics, San Juan Capistrano, Calif). This rapid PTH immunoradiometric assay was used intraoperatively for all parathyroid explorations. All patients had peripheral venous blood samples obtained at the induction of general anesthesia and 7 minutes after excision of all suspected hyperfunctioning parathyroid tissue. Results of the rapid PTH immunoradiometric assays were generally available within 20 to 25 minutes.

All patients with suspected parathyroid adenoma underwent a technetium-99m sestamibi-directed unilateral cervical exploration with intraoperative rapid PTH assay sampling. A contralateral neck exploration and biopsy of at least 1 normal gland was also performed in all patients with adenoma to assess the validity of the intraoperative rapid PTH assay values. Patients with multiple gland hyperplasia underwent standard bilateral cervical explorations with rapid PTH sampling to confirm removal of all hyperfunctioning parathyroid tissue. All patients were followed up for a minimum of 9 months and were evaluated in the postoperative period for resolution of clinical signs and symptoms as well as for normalization of serum calcium and PTH levels.

confirmed in 32 patients, with 10 patients demonstrating multiple gland hyperplasia. In 1 patient, the histologic diagnosis could not be established because no parathyroid tissue was identified intraoperatively. There were no cases of multiple adenoma or carcinoma. No deaths or significant operative complications were encountered.

Thirty (94%) of the 32 patients with histologically confirmed single-gland disease had the adenoma correctly localized preoperatively to either the right or left side of the neck by technetium-99m sestamibi imaging. In 1 patient, the preoperative sestamibi scan was interpreted as inconclusive, and in the remaining patient the scan was inaccurate. This latter patient’s adenoma was removed from the contralateral aspect of the neck. In the 32 patients with adenomas, the mean intraoperative preexcision rapid PTH assay value was 27.5 pmol/L (261 pg/mL) (median, 20.5 pmol/L [195 pg/mL]; range, 10.0-123.9 pmol/L [95-1173 pg/mL]). The mean intraoperative postexcision rapid PTH assay value in these patients was 6.4 pmol/L (61 pg/mL) (median, 4.9 pmol/L [47 pg/mL]; range, 0.9-17.2 pmol/L [9-163 pg/mL]). The mean decrease in rapid PTH levels for the 32 patients was 70% (median, 77%; range, 52%-93%). In all the patients with adenoma, the rapid PTH sample obtained 7 minutes after removal of the adenoma demonstrated a decrease exceeding 50% when compared with the preexcision rapid PTH sample, indicating removal of all hyperfunctioning parathyroid tissue. These intraoperative results were corroborated with those of an exploration of the contralateral aspect of the neck that demonstrated no abnormalities and a biopsy specimen of at least 1 normal gland, together with normalization of postoperative serum calcium and PTH levels. None of the patients have demonstrated persistent or recurrent hyperparathyroidism on follow-up.

Of the 10 patients identified as having multiple gland hyperplasia, 5 were diagnosed as having secondary hyperparathyroidism, 3 as having multiple endocrine neoplasia syndrome, and 2 as having tertiary hyperparathyroidism. A total of 11 parathyroid explorations were performed on these 10 patients. One patient presented to us having previously undergone a 4-gland parathyroidectomy with forearm autotransplantation for secondary hyperparathyroidism. A decrease in serum PTH levels was noted during the postoperative period; however, subsequent determinations 6 years after the above procedure indicated a progressive rise in serum PTH values. It was initially thought that this rise in PTH was due to hyperfunctioning parathyroid tissue in the forearm, and the patient consequently underwent forearm exploration with removal of all identifiable parathyroid tissue. During the course of the procedure, the patient’s PTH levels were noted to increase from a preexcision value of 62.5 pmol/L (594 pg/mL) to a postexcision value of 124.7 pmol/L (1184 pg/mL), indicating the presence of persistent hyperfunctioning parathyroid tissue. The patient subsequently underwent technetium-99m sestamibi imaging together with magnetic resonance imaging of the neck, the findings of which suggested residual parathyroid tissue within the left lower aspect of the neck (Figure 1 and Figure 2). A cervical exploration was performed, and a fifth hyperplastic parathyroid gland was identified and removed. The rapid intraoperative PTH levels obtained during the cervical exploration confirmed removal of all hyperfunctioning parathyroid tissue and demonstrated a decline from a preexcision value of 152.7 pmol/L (1450 pg/mL) to a postexcision value of 32.7 pmol/L (311 pg/mL) (a 79% decrease from preexcision sample). This patient has been followed up for 12 months without evidence of recurrence. The mean intraoperative preexcision rapid PTH level for the remaining 9 patients with multiple gland hyper-
plasia (9 parathyroid explorations) was 69.3 pmol/L (658 pg/mL) (median, 59.0 pmol/L [560 pg/mL]; range, 19.6-145.8 pmol/L [186-1385 pg/mL]). The mean intraoperative postexcision rapid PTH level was 17.7 pmol/L (168 pg/mL) (median, 6.0 pmol/L [57 pg/mL]; range, 2.3-11.6 pmol/L [22-110 pg/mL]). The mean percentage of decrease between the intraoperative preexcision and postexcision rapid PTH levels was 90% (median, 90%; range, 82%-95%). In all 9 patients, the 7-minute postexcision intraoperative rapid PTH sample demonstrated a decline of greater than 50% and indicated removal of all hyperfunctioning parathyroid tissue. The rapid PTH assay values were corroborated with intraoperative findings as well as with postoperative normalization of serum PTH levels and resolution of clinical symptoms. All patients with multiple gland disease have been followed up for a minimum of 12 months.

Rapid intraoperative PTH determinations have also proved to be accurate in the setting of normal findings on parathyroid exploration. One patient presented to us with persistent primary hyperparathyroidism after reportedly undergoing a subtotal thyroidectomy and a subtotal parathyroidectomy at an outside institution. The findings of analysis of a permanent histologic section from this procedure did not confirm the presence of parathyroid tissue. The patient continued to demonstrate elevated total serum calcium, urine calcium, and PTH levels postoperatively. A technetium-99m sestamibi scan and a magnetic resonance imaging scan of the neck and mediastinum were subsequently obtained but did not demonstrate the presence of any parathyroid tissue. A cervical exploration was performed, but no parathyroid tissue was identified despite an extensive bilateral dissection. Rapid intraoperative PTH sampling at induction (12.4 pmol/L [118 pg/mL]) and at closing (22.1 pmol/L [210 pg/mL]) indicated the presence of persistent hyperfunctioning parathyroid tissue. This was substantiated postoperatively by continuing symptoms and persistent elevations in total serum calcium and PTH levels, lending additional support to the efficacy of this procedure. Venous angiography with selective venous sampling was recommended, but the patient refused any further intervention and was subsequently unavailable for follow-up.

**COMMENT**

The rapid PTH immunoradiometric assay has, in our experience, accurately reflected removal of all hyperfunctioning parathyroid tissue in every patient evaluated thus far. Although originally developed for use in patients with multiple gland hyperplasia, rapid intraoperative PTH assays, when combined with the improved accuracy of preoperative localization with technetium-99m sestamibi imaging, can be very helpful in permitting directed parathyroid explorations in patients with hyperparathyroidism secondary to an adenoma. Considerable debate has raged over the efficacy and wisdom of performing unilateral vs bilateral cervical exploration in preoperatively localized parathyroid adenoma. Advocates of bilateral cervical exploration have generally cited the possibility of missing multiple adenomas or unrecognized hyperplasia as reasons for performing bilateral cervical exploration, whereas advocates of unilateral exploration have argued that a unilateral exploration performed in conjunction with preoperative localization results in decreased operative time and cost, while also minimizing surgical morbidity. A method to detect residual hyperfunctioning parathyroid tissue, such as that described herein, will minimize the risk of missing multiple gland disease. A directed unilateral cervical exploration based on preoperative localization results combined with intraoperative rapid PTH determinations appears to be effective in reducing the possibility of overlooking multiple gland disease, while also minimizing operative time, cost, and potential morbidity. Rapid biochemical confirmation of removal of all hyperfunctioning parathyroid tissue provides the parathyroid sur-
geon with a greater degree of confidence that multiple adenomas or unrecognized hyperplasia has not been overlooked despite a unilateral cervical exploration.

The short half-life of PTH (roughly 2 to 5 minutes) allows peripheral blood samples to be obtained intraoperatively for rapid PTH assay testing 7 minutes after excision of all suspected hyperfunctioning tissue. Kao et al. have demonstrated that the most precipitous decrease in rapid PTH assay values occurs 5 minutes after excision of all hyperfunctioning parathyroid tissue and that the values generally decrease to less than 30% of the basal values. Subsequent measurements at 10 and 20 minutes after excision of all hyperfunctioning parathyroid tissue demonstrated a less dramatic decrease from the 5-minute postexcision value. In accordance with previous reports, a decrease of greater than 50% in the postexcision rapid PTH assay level as compared with the preexcision level was thought to be indicative of the removal of all hyperfunctioning parathyroid tissue.

Although comparisons of operative time and cost were not the intent of this study, indications are that roughly 30 to 35 minutes would have been saved had exploration been limited to one side of the neck in patients with single-gland disease. The total laboratory cost of each rapid PTH immunoradiometric assay at our institution is $150; therefore, the minimal total laboratory costs for the rapid PTH assays performed during each procedure were $300. At our institution, 30 minutes of operating room and anesthesia charges amount to $429 and $126, respectively. The total operating room charges for 30 minutes therefore amount to $555.

The rapid intraoperative PTH immunoradiometric assay is clearly of benefit in the surgical treatment of patients with multiple gland hyperplasia. This method serves as a valuable intraoperative adjunct to biochemically confirm removal of all hyperfunctioning parathyroid tissue. This procedure is particularly useful in patients who may harbor an abnormal number of glands or in patients in whom parathyroid glands are ectopically located.

With respect to the surgical treatment of patients with parathyroid adenoma, it is our impression that the use of this procedure in concert with preoperative localization will ultimately lead to the routine performance of directed unilateral cervical exploration. Our results with preoperative localization are consistent with those mentioned in more recent reports concerning the accuracy of preoperative localization with technetium-99m sestamibi imaging in patients with primary hyperparathyroidism. An ideal clinical scenario with which to confirm the efficacy of this procedure would be one in which a directed unilateral exploration is performed on a patient with unrecognized double adenoma. In this scenario, one adenoma is removed in conjunction with biopsy of a normal suppressed gland. The patient continues to demonstrate an elevated intraoperative PTH level and, as a result, an exploration of the contralateral aspect of the neck is performed, with the subsequent identification and removal of the second adenoma, followed by a decrease in PTH levels. Based on our experience with this intraoperative rapid PTH assay, we are confident that in the near future parathyroid surgeons will be able to limit their explorations for hyperparathyroidism secondary to adenoma to one side of the neck, with the added benefit of having biochemical assurance of the removal of all hyperfunctioning tissue. It is our intention to use this assay routinely in all patients requiring parathyroid exploration in order to increase our experience with this procedure and to further support the surgical philosophy of limited cervical exploration in patients with suspected single-gland parathyroid disease.

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Corresponding author: Phillip K. Pellitteri, DO, Department of Otolaryngology–Head and Neck Surgery, Penn State Geisinger Health System, Danville, PA 17822-1333.

REFERENCES