



Quick Intraoperative Parathyroid Hormone Assay: Surgical Adjunct to Allow Limited Parathyroidectomy, Improve Success Rate, and Predict Outcome

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Abstract. Intraoperative parathyroid hormone (PTH) assay (QPTH) has made possible less invasive operative approaches in the treatment of primary hyperparathyroidism with stated advantages. When compared to the traditional bilateral neck exploration (BNE), only the targeted, hypersecreting gland is excised, leaving in situ non-visualized but normally functioning parathyroids. The QPTH-guided limited parathyroidectomy (LPX) must be able to identify multiglandular disease (MGD), predict a successful outcome, and have a low recurrence rate. In our series, 421 patients who underwent LPX were compared to 340 undergoing BNE; all operative failures and patients followed for 6 months or longer were included. Operative failure occurred if serum calcium and PTH levels were elevated within 6 months of parathyroidectomy. Multiglandular disease was defined in the LPX group as more than one gland excision guided by QPTH or operative failure after removal of a single abnormal gland; in the BNE group it was defined as excision of more than one enlarged gland. Recurrence was defined as elevated calcium and PTH after 6 months of eucalcemia. Operative failure and MGD rates were compared using chi-squared analysis. The method of Kaplan-Meier and the log-rank test were used to compare recurrence rates. Operative success was seen in 97% of LPX patients and in 94% of the BNE group ($p = 0.02$). Multiglandular disease was identified in 3% of LPX patients and 10% of BNE patients ($p < 0.001$). There was no statistical difference in the overall recurrence rates ($p = 0.23$). The QPTH-guided parathyroidectomy identifies MGD and allows an improved success rate with the same low recurrence rate when compared to the results of BNE.

Since 1996, when intraoperative parathyroid hormone assays (QPTH) became commercially available, many surgeons in different parts of the world have reported their parathyroidectomy results using this surgical adjunct with varying degrees of success. It is well accepted that intraoperative parathyroid hormone assays can accurately measure the hormone level in plasma and that these levels decrease rapidly when all hypersecreting parathyroid glands are excised. However, the reported divergent success rates, along with

overlooked or missed multiglandular disease (MGD), unrecognized complete excision of the identified hyperfunctioning gland, and the added expense of this laboratory test have prompted some authors to doubt the usefulness of QPTH as a surgical adjunct.

Our group has previously reported that most of the criticisms of intraoperative hormone assays are criteria related. This includes different timing for intraoperative sample collection, the requirement of more strict hormone dynamics for predicting outcome, or the surgeon's ignoring an adequate drop in the hormone level after removal of a single hypersecreting gland, leading to unnecessary continued neck exploration and excision of other "enlarged" parathyroids based on size alone [1, 2].

The purpose of this study was to answer the following questions about the quick intraoperative PTH assay:

- Why is it needed?
- How does it work?
- How accurate is it?
- What are the criticisms?
- How has it changed our management of sporadic primary hyperparathyroidism?

The first four questions are addressed in the discussion of this manuscript with previously reported numbers upgraded and summarized from our ongoing database of 925 sporadic primary hyperparathyroid (SPHPT) patients undergoing parathyroidectomy in a single institution. The change in our management of patients with this disease is described and supported with new data analyzing operative success and late recurrence rates found with two different operative approaches.

Methods

With the help of cervical ultrasonography, Tc-m99-sestamibi nuclear scanning, or differential jugular venous hormone sampling for localization, we use a targeted or focused operative approach in SPHPT patients. Secondary, tertiary, familial hyperparathyroid, and multiple endocrine neoplasia (MEN), patients were excluded.

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Limited parathyroidectomy (LPX) is usually performed through a small (3 cm) incision under local or light general anesthesia with dissection directed at the suspected hypersecreting gland. After mobilization of the abnormal gland, the second peripheral plasma sample (pre-excision level) is obtained just before the blood supply is taken and excision is completed. No more exploration is done, and there is no further attempt at visualization of the in situ parathyroid glands. Wound closure is usually completed by the time the 10-minute parathyroid (PTH) sample is reported and, depending on the hormone dynamics, the procedure is finished or the wound is reopened and exploration of the neck is continued until all hypersecreting parathyroid glands have been found and excised as confirmed by a significant drop in the hormone level [3].

Limited parathyroidectomy was attempted on all patients, whether the preoperative localization studies were positive or not. When the hyperfunctioning gland was not obvious, as was the case in patients with multinodular goiter with equivocal scans and unclear ultrasound studies, QPTH often suggested the side of the neck to explore, based on differential jugular venous sampling.

Two assays were used in this study: Future Diagnostics (Wijchen, the Netherlands), and Nichols Institute Diagnostics (San Juan Capistrano, CA). Hormone dynamics, measured during the procedure, guided all parathyroidectomies during this 10-year period, except in three cases where a mechanical breakdown prevented the use of the assay.

The definition of operative success is eucalcemia for 6 months or longer following parathyroidectomy. Operative failure is defined as hypercalcemia and elevated PTH levels above the normal range for the reporting laboratory any time during this 6-month period. Recurrent hyperparathyroidism is defined as hypercalcemia and elevated PTH levels occurring after a successful parathyroidectomy, documented by eucalcemia for 6 months or longer.

To determine the operative success rate of parathyroidectomy, all patients were followed at least 6 months or identified as an operative failure by having hypercalcemia and elevated PTH within this time frame. The operative success, evidence of MGD, and recurrence rates in 421 SPHPT patients followed for 6 months or longer were compared to those of 340 previously reported patients undergoing bilateral neck exploration (BNE) [2]. All patients with hypercalcemia and elevated PTH levels within 6 months of parathyroidectomy were considered operative failures and were included in this study.

Recurrence was calculated after 6 months of eucalcemia postoperatively. Recurrence distributions were estimated with the method of Kaplan and Meier. The log-rank test was used to compare recurrence among the two groups of patients. Operative failure rates and the prevalence of MGD were compared using chi-squared analysis. Analyses were performed with the statistical software package Statistix version 8.0 (Analytical Software, Tallahassee, FL). A p value < 0.05 was considered statistically significant.

Results

Since 1993, 528 consecutive SPHPT patients have had LPX at our institution. There were 482 patients undergoing parathyroidectomy for the first time and 46 requiring reoperations for persistent or recurrent disease after parathyroidectomy at another institution. In the LPX group, there were 421 patients who were followed for 6 months or longer and/or were identified as operative failures.

Eleven patients (3%) were recognized as operative failures. When compared to a similar but historical group of 397 BNE patients where 20 operative failures were noted out of 340 (6%) with adequate follow-up, the LPX group had fewer operative failures ($p = 0.02$).

Because patients from other institutions undergoing reoperative parathyroidectomy ($n = 59$) could not be adequately evaluated for MGD, the incidence is reported in 702 (380 LPX, 322 BNE) patients who had undergone an initial parathyroidectomy in our institution. Multiglandular disease was found in 12 (3%) patients in the LPX group. When compared to the BNE group, where 32 (10%) of the patients undergoing their initial operation were found to have more than one gland involved, the difference was statistically significant ($p < 0.001$). It is important to note that in the LPX group, QPTH identified all but one patient (false positive, FP) with multiple hypersecreting glands. In the 12 patients with MGD, there were 26 QPTH predictions, 24 of which were correct (9 TP, 15 TN) and two were incorrect (1 FP, 1 FN) giving the assay a sensitivity, specificity, and overall accuracy of 90%, 94%, and 92%, respectively.

We have been able to follow the LPX group for a mean of 35 months (range: 6–122 months) and the BNE group for a mean of 123 months (range: 6–409 months). The overall number of recurrences for the LPX and the BNE groups involved 6 and 13 patients, respectively. To date, there is no difference in the overall recurrence rates ($p = 0.23$). Six patients in each group have had recurrent hyperparathyroidism within 90 months of parathyroidectomy (Fig. 1).

Discussion

Why Is QPTH Needed?

The explanation for why an intraoperative hormone assay is needed is best illustrated in the actual case report that initiated the incorporation of this surgical adjunct as part of our current operative procedure.

In 1990, a prominent member of our hospital staff was referred with a secure diagnosis of primary hyperparathyroidism. Although, at age 50, she was asymptomatic and working full-time as an operating room supervisor in our busy public hospital, her serum calcium levels were consistently 13 mg/dl with an intact PTH level above 200 pg/ml and normal renal function. A parathyroidectomy was performed with a complete BNE to search for all four parathyroid glands, as was our customary operative approach at that time. The operative findings were gratifying in that a single enlarged parathyroid gland ($2.2 \times 1.0 \times 0.4$ cm) was found and excised. Continued exploration on the contralateral side identified another normal-sized parathyroid gland, which was biopsied for histological confirmation. Careful bilateral exploration of the usual anatomical locations of parathyroid glands, including the upper mediastinum, did not reveal any other parathyroid tissue. With excision of one enlarged gland, the finding of one normal-sized gland in the contralateral neck, and thorough exploration of the cervical area without finding any other enlarged parathyroid, a success rate of 94% could be expected, and the procedure was finished.

Unfortunately, this very visible patient was an operative failure, with her postoperative serum calcium continuing in the 12.5 mg/dl range with a PTH level of 200 pg/ml.

This was not the kind of operative failure you can hide in the

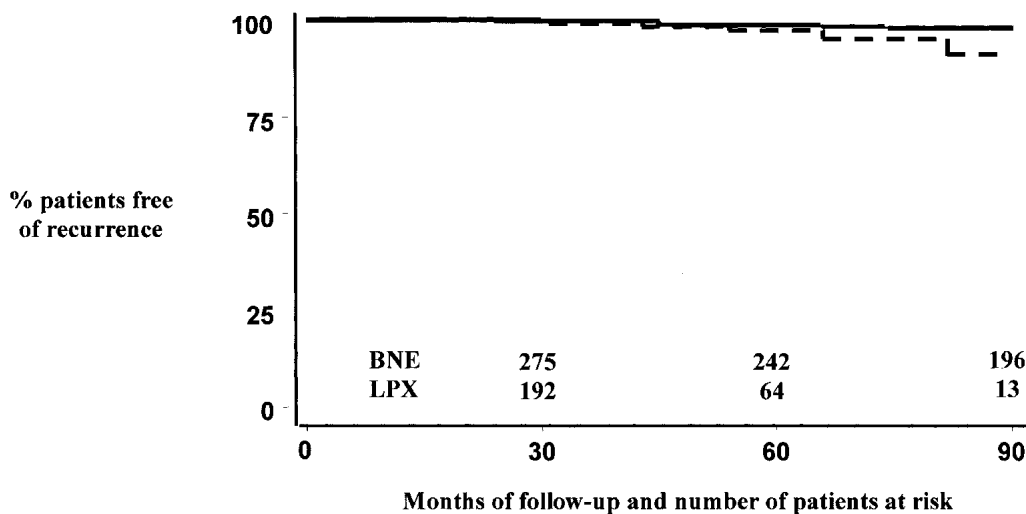


Fig. 1. Kaplan-Meier recurrence curves comparing patients who underwent bilateral neck exploration (BNE; solid line) or limited parathyroidectomy (LPX; dashed line); *p* = ns. The numbers represent the eligible or at-risk patients followed.

community. Everyone knew what had happened, and the embarrassment of the surgeon was real. How could an operative failure such as this have been prevented? What we needed was a quantitative test to measure parathyroid gland hyperfunction: a test that would confirm when all hypersecreting parathyroid tissue had been removed and prevent the surgeon from overlooking MGD during parathyroidectomy. Remembering Nussbaum's suggestion at the American Association of Endocrine Surgeons meeting in 1987 that his new two-site antibody assay which measured the intact parathyroid hormone might be useful as an intraoperative adjunct in parathyroidectomy, we began modifying his immunoradiometric assay by heating and shaking the sample to speed the reaction. With this modification, we could measure serum PTH in 15 minutes. Rapid results are essential to be useful to the operating surgeon, so by miniaturizing the equipment and mobilizing it on a portable cart, the assay could be taken in or near the operating room as a real-time surgical adjunct.

What happened to the index case? Four months after the failed initial parathyroidectomy, a second overlooked, enlarged parathyroid gland, hidden within the lobe of the thyroid, was excised with a thyroid lobectomy. The parathormone level, measured during the procedure, quickly dropped significantly, predicting a return to eucalcemia.

By determining whether all hypersecreting parathyroid glands have been excised or not after excision of any suspected tissue, this surgical adjunct can be used to prevent overlooked MGD during parathyroidectomy. This is why QPTH is needed.

How Does QPTH Work?

Based on the two-site antibody immunoradiometric assay for measuring intact PTH described by Nussbaum and co-workers in 1987 [4], modifications including replacing radioisotopes with a chemiluminescent light source along with sample heating and shaking to speed the reaction, have been used in several commercially available assays [5]. If the assay is performed in or in close vicinity of the operating room, the surgeon can expect the hormone level to be reported in 8-15 minutes from the time each sample is taken [6]. Most commercially available assays are sensitive, accurate, and correlate well with the standard assays used for parathormone levels in a nonoperative setting.

Prediction of postoperative calcium levels by intraoperative hormone measurements essentially depends on whether there is a dynamic change in the hormone level once all hypersecreting glands are removed. We have found that the most accurate criterion for predicting the outcome of parathyroidectomy is a drop of 50% or more from the highest parathormone level from either the pre-incision or pre-excision level, measured 10 minutes after the suspected gland is excised (Miami criterion). The reason for measuring the two early samples is that during dissection of a suspected hyperfunctioning gland, the peripheral hormone level may increase significantly from the preoperative level caused by manipulation of the gland, or if the blood supply is compromised, the PTH level may decrease rapidly and be measured below the starting pre-incision value at the pre-excision sample time. Figure 2 shows a graph of the hormone dynamics in a patient with a single hypersecreting gland that was excised, followed by a significant fall in the hormone level predicting postoperative eucalcemia. These are the data the surgeon should receive intraoperatively, with the percentage drop from the highest value obtained before gland excision. It is the surgeon's responsibility to assure good peripheral blood access, either with an in-dwelling venous catheter or an arterial line, and to oversee the sample timing at the proper stages of the procedure. We think peripheral sampling is more accurate than jugular vein sampling, in that plasma drawn from close proximity to a hypersecreting gland will often give higher values. Use of the jugular site is sometimes useful in differential cervical vein sampling for localizing a "hard-to-find" gland, but is not as consistent in measuring PTH levels as the peripheral site when evaluating complete excision of all hyperfunctioning tissue with the criterion used in this series of patients [3].

As shown in Figure 3, the percentage hormone drop from the highest recorded level did not meet our criterion for complete excision of all hypersecreting tissue after the excision of two enlarged glands. This represents a patient with MGD in whom the hormone level did not have an adequate drop until three hyperplastic glands were removed. When the hormone level fails to drop more than 50% from the highest pre-incision or pre-excision level 10 minutes after excision of a suspected hypersecreting parathyroid gland, the process must be repeated after the search for and removal of another abnormal gland until the criterion is met. When used in this manner, once a significant drop in the hormone level is accom-

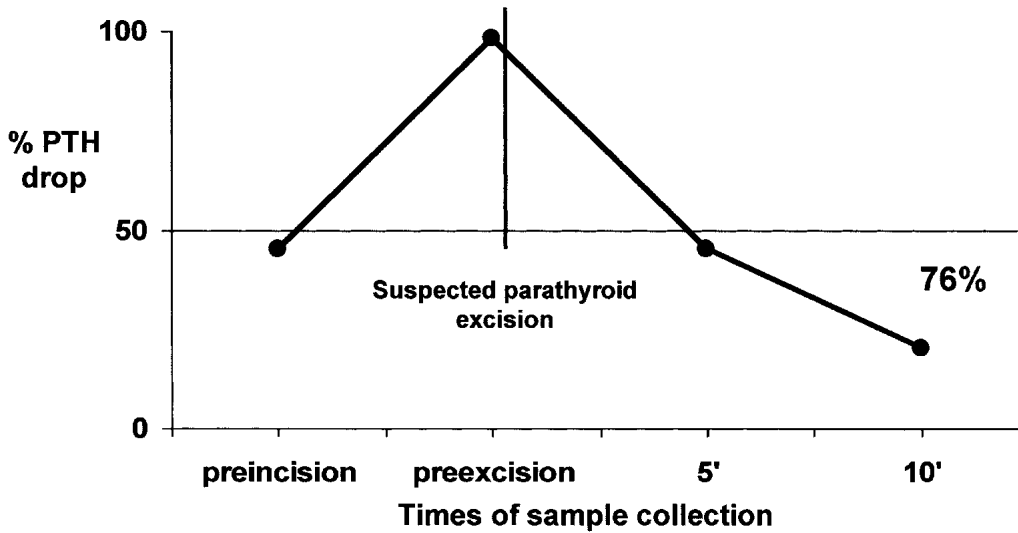


Fig. 2. Graph of intraoperative parathormone dynamics demonstrating a significant fall in the hormone level from the pre-excision plasma sample following excision of a single hypersecreting parathyroid gland predicting postoperative eucalcemia. PTH, parathyroid hormone; 5', five minutes; 10', ten minutes.

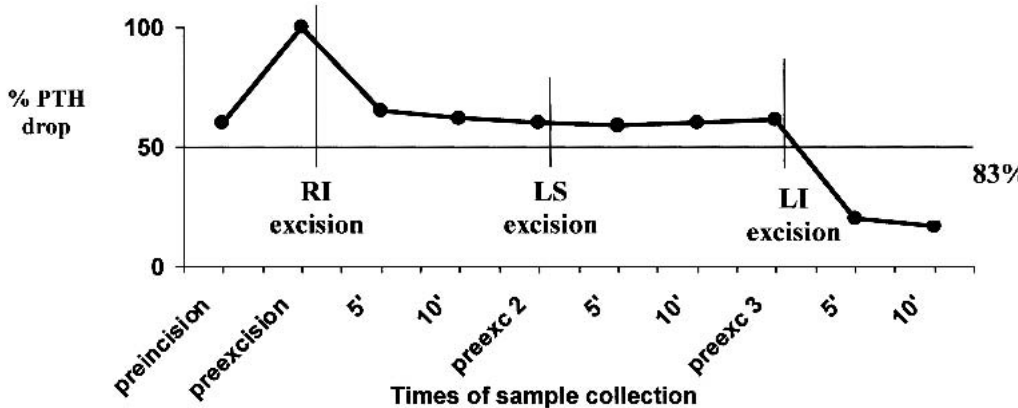


Fig. 3. Graph of intraoperative parathormone dynamics showing less than a 50% drop from the highest PTH level after excision of two abnormal glands, signaling inadequate excision of all the hypersecreting tissue. The significant drop after excision of the third hyperplastic gland predicted postoperative return of eucalcemia. RI: right inferior; LS: left superior; LI: left inferior; preexc: preexcision.

plished, the assay will predict postoperative eucalcemia and operative success. However, in the rare patient with hard-to-find glands requiring a long, complicated exploration and multiple hormone measurements, a pre-excision sample is not always available before each excision. In this case, surgical judgment should be exercised by considering all timed assay results obtained during the procedure in relation to the operative findings.

How Accurate Is QPTH?

The accuracy of QPTH using the specific Miami criterion is based on the intraoperative prediction of postoperative serum calcium levels. Operative success is defined as patients returning to eucalcemia, which must be measured and found to be within normal range for 6 months or longer following parathyroidectomy [7-10]. The definitions used to determine the predictability of the assay with our criterion are shown in Table 1. If a decrease in the PTH level of 50% or more from the highest level measured from either the pre-incision or pre-excision plasma sample taken 10 minutes after removal of a suspected abnormal parathyroid gland resulted in the patient's maintaining a normal calcium level for 6 months, then the test was true positive (TP). If the same PTH drop occurred during parathyroidectomy, and the patient had persistent hypercal-

Table 1. Definitions used to determine the accuracy of QPTH with the Miami criterion in predicting postoperative calcium levels.

	QPTH drop \geq 50%	QPTH drop < 50%
Eucalcemia (\geq 6 months)	True positive	False negative
Hypercalcemia (< 6 months)	False positive	True negative

A true negative fall of < 50% PTH level indicated intraoperatively that more hypersecreting tissue was still present requiring more excision until a significant fall occurred or continued postoperative hypercalcemia was predicted.

QPTH: intraoperative parathyroid hormone assay.

cemia within 6 postoperative months, then the QPTH prediction was incorrect, and the test was labeled false positive (FP).

On the other hand, if the PTH level failed to drop more than 50% at the specific 10 minute sample time from the highest index level before gland excision, and the patient was cured with demonstrated eucalcemia for 6 months, then QPTH was labeled false negative (FN). If there was a delayed drop in the hormone level occurring later than the criterion stated time of 10 minutes, the QPTH was labeled FN, even though eucalcemia was observed postoperatively. A true negative (TN) QPTH result occurred whenever the hormone dropped less than 50% from the highest level at the 10-minute sample time. This indicated to the surgeon that all hyper-

secreting parathyroid tissue had not been removed, as in the case of MGD, or that the excised tissue was not the hyperfunctioning gland as suspected. This failure of the hormone to have an adequate drop mandated continued exploration until all abnormal hypersecreting parathyroid tissue had been removed, or without a significant drop, QPTH predicted operative failure with continued postoperative hypercalcemia.

As we have previously shown, QPTH with the Miami criterion is a very accurate predictor of outcome [1, 2]. The data described in this report are updated from our previous articles and now includes 492 QPTH predictions in 421 patients who remained eucalcemic for 6 months or longer or who were identified as operative failures with persistent hypercalcemia and elevated PTH levels. There were 480 correct intraoperative predictions: 401 TP and 79 TN. There were also 12 incorrect predictions: 3 FP and 9 FN. Therefore, QPTH using the Miami criterion predicted postoperative calcium levels with a sensitivity of 98%, a specificity of 96%, a positive predictive value of 99%, a negative predictive value of 90%, and an overall accuracy of 98%.

What Are the Criticisms of QPTH?

As with many new technical advances, intraoperative hormone assays are expensive. To cut costs of multiple measurements, some surgeons use a protocol that calls for only one “baseline” sample before the abnormal gland is excised. As detailed above, this does not allow for a decrease or increase in the peripheral hormone level during manipulative dissection of a hypersecreting gland. Under these circumstances, the 50% drop is often not achieved with excision of the hypersecreting gland. This results in a high FN rate and causes too many unnecessary continued neck explorations [11]. As we have shown, this criterion results in a 12%–13% increase in the FN rate compared to QPTH using the recommended criterion which incorporates both a pre-incision and a pre-excision sample from which to measure the decrease in PTH [1].

Another criticism is that QPTH gives too many FP predictions. Some surgeons have reported excision of a single hypersecreting gland followed by a significant drop in the hormone level predicting a return to eucalcemia. However, these authors continue with a BNE with the finding of another “large” gland which is also excised. They report that QPTH was FP and missed a second adenoma or MGD. These same authors report a MGD rate of 17%–30% in patients with SPHPT although there is no evidence that the second “large” gland was hypersecreting or contributing to the hyperparathyroid disease [12, 13].

The criticism that QPTH gives too many false positives and false negatives is criteria-dependent. With QPTH and the criterion used in this series of 421 patients, we report a FP rate of 1% and a FN rate of 2%.

How Has QPTH Changed Our Management of SPHPT?

With the ability to accurately predict the outcome of parathyroidectomy, namely, postoperative serum calcium levels based on intraoperative PTH dynamics, several new operative approaches have been described [14–17]. These new operative innovations are designed to improve the traditional, more invasive BNE by not having to identify all normally functioning parathyroid glands. Instead, QPTH allows the parathyroidectomy to be based solely on the hypersecretion of an abnormal gland or glands. These less invasive

parathyroidectomy techniques offer several published advantages [2, 18]. These advantages include excision of only the hypersecreting gland(s) without disturbing the remaining normally functioning parathyroids, help with localization of hard-to-find glands, successful unilateral neck exploration, the use of a small incision and short operating time, local or light general anesthesia, and same-day discharge with less hospital cost. With the help of good localization studies and the intraoperative PTH assay, our group has used a targeted approach, or limited parathyroidectomy (LPX), since 1993. We have shown an improved operative success rate with LPX compared to similar patients undergoing the traditional operation with BNE [2]. However, to justify this change in operative management, which leaves behind some non-visualized and presumed enlarged but not hypersecreting parathyroid glands, the question of whether this operative approach may give an increased incidence in recurrent hyperparathyroidism must be answered.

In this study, we address these critical points in our experience with 528 patients undergoing LPX since 1993 by comparing the operative outcome with 397 historical BNE parathyroidectomy patients from the same institution. We have shown that QPTH with the Miami criterion has accurately identified MGD when present, has improved the operative success rate compared to historical patients undergoing the BNE from the same institution, and has maintained the same low recurrence rate to date. Only more time will determine if LPX will continue to have the same recurrence expectation as found with the traditional operative procedure where all enlarged glands are excised based on the surgeon’s judgment. However, unless a higher recurrence rate becomes evident in later years, the intraoperative PTH assay guided parathyroidectomy appears to have some distinct advantages over the traditional parathyroidectomy.

Conclusions

The quick intraoperative measurement of PTH dynamics has changed our management and significantly improved the operative approach in patients undergoing parathyroidectomy for SPHPT. With a better operative success rate and a similar low recurrence rate to date compared to patients undergoing the traditional parathyroidectomy with BNE, we suggest that this surgical adjunct may be helpful to surgeons treating this disease.

Résumé. Le dosage peropératoire de PTH (DPHT) a permis des approches opératoires moins invasives dans la prise en charge de l’hyperparathyroïdie primitive avec certains avantages. Comparée à l’exploration traditionnelle bilatérale du cou (ETB), seules les glandes hypersécrétantes, ainsi ciblées, sont excisées, laissant in situ les parathyroïdes non-visualisées, mais normo-fonctionnelles. Lors de la parathyroïdectomie élective guidée (PEG) par DPHT, on doit néanmoins pouvoir détecter la maladie multiglandulaire (MMG), prédire une évolution favorable et s’assurer d’un taux de récurrence peu élevé. 421 patients qui ont eu une PEG ont été comparés à 340 patients ayant eu une ETB; tous les échecs opératoires et les patients suivis pour au moins six mois ont été inclus. On parle d’échec opératoire lorsque la calcémie et les taux de PTH restent élevés six mois après la parathyroïdectomie. La MMG a été suspectée lorsque la chute de PTH était insuffisante ou un échec opératoire après excision d’une seule glande anormale dans le groupe PEG et par l’exérèse d’une glande augmentée de volume dans le groupe ETB. La récurrence a été définie par une calcémie et un taux de PTH élevés après six mois de normocalcémie. L’échec opératoire et les taux de MMG ont été comparés entre eux par l’analyse Chi². La méthode de Kaplan-Meier et le test de Log-rank a été utilisé pour comparer les taux de récurrences. Le succès opératoire a été constaté chez 97% des patients du groupe PEG et chez 94% du groupe ETB ($p = 0.02$). La MMG a été identifiée chez 3% du groupe PEG et chez 10% des

patients du groupe ETB ($p < 0.001$). Il n'y avait aucune différence statistiquement significative du taux global de la récurrence ($p = 0.23$). La PEG permet d'identifier la MMG, le taux de réussite est supérieur, et le taux de récurrence est similaire à ceux de l'ETB.

Resumen. La inmediata determinación intraoperatoria de la PTH (QPTH) ha permitido desarrollar técnicas quirúrgicas más adecuadas y poco agresivas para el tratamiento del hiperparatiroidismo primario. La tradicional exploración mediante cervicotomía bilateral (BNE) ha sido sustituida por la extirpación exclusiva de la glándula hipersecretora, permaneciendo las restantes glándulas paratiroides in situ sin necesidad alguna de visualizarlas mediante disección quirúrgica. La paratiroidectomía limitada (LPX) dirigida gracias a la determinación inmediata intraoperatoria de la parathormona (QPHT), debe permitir también la identificación de una afectación multiglandular (MGD), proporcionando buenos resultados con escaso número de recidivas. Se compararon 421 pacientes tratados mediante paratiroidectomía limitada (LPX) frente a 340 sometidos a cirugía convencional (BNE). Se registraron todos los fracasos quirúrgicos observados tras seguimiento de los pacientes de seis o más meses. Consideramos que la cirugía ha fracasado cuando los niveles séricos de calcio y de PTH permanecen elevados dentro de los seis meses tras paratiroidectomía. Se consideró que existía una afectación multiglandular (MGD) cuando el descenso de la PTH fue inadecuado, cuando se produjo un fracaso quirúrgico tras la extirpación de una glándula anormal en el grupo LPX o cuando en el grupo BNE se extirparon glándulas hipertróficas. La recidiva viene dada por calcemias y PTH elevadas tras 6 meses de normocalcemia. Los fracasos operatorios y la tasa de afectación multiglandular (MGD) se compararon utilizando la Chi al cuadrado. El método de Kaplan-Meier y el long rank test se utilizó para comparar la tasa de recidivas. El 97% de los pacientes del grupo LPX y el 94% de los del grupo BNE fueron intervenidos con éxito ($p = 0.02$). Afectación multiglandular se observó en el 3% de pacientes del grupo LPX y en el 10% del grupo BNE ($p < 0.001$). No constatamos diferencias estadísticamente significativas en el conjunto del porcentaje de recidivas ($p = 0.23$). La paratiroidectomía teledirigida mediante el QPTH permite identificar una afectación multiglandular (MGD), cursando con similar porcentaje de curaciones y con la misma escasa tasa de recidivas que la cervicotomía bilateral convencional (BNE).

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