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Mini review

Section 1. Parathyroid
Intraoperative quick parathyroid hormone assay in the surgical management of hyperparathyroidism

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Abstract

Intraoperative quick parathyroid hormone (QPTH) assay is claimed to prevent failure during parathyroidectomy for hyperparathyroidism. The causes of operative failure have included multiglandular disease, ectopic parathyroid glands, supernumerary parathyroid glands, errors in frozen section evaluations, and missed diagnosis. A QPTH assay has been recognized as a useful method of determining whether hyperfunctioning tissues have been completely excised. However, an intraoperative QPTH assay may fail to detect the presence of double parathyroid adenomas. Use of this assay in conjunction with preoperative and intraoperative localization studies has led to the advocacy of more directed cervical procedures, such as limited, video-assisted, and endoscopic parathyroidectomy.

Keywords: Parathyroid hormone; Hyperparathyroidectomy; Quick assay

1. Introduction

Until recently, there was a debate as to whether unilateral or bilateral neck exploration was preferable in primary hyperparathyroidism. Surgeons who advocated bilateral neck exploration believed that it should be the standard approach, because it is safe and greatly reduces the chances of missing a second adenoma. Some endocrine surgeons, however, have advocated a unilateral approach for initial parathyroid exploration to lower the risk of recurrent nerve injury and hypoparathyroidism as well as to reduce the operation time [1]. Innovations such as the intraoperative quick parathyroid hormone (QPTH) assay [2] and sestamibi scintigraphy [1,2] have allowed the development of minimally invasive parathyroidectomy [3], limited parathyroidectomy [4], and endoscopic parathyroidectomy [5], and several investigators have reported high success rates using these techniques, with reductions in incision length, operation time, and length of hospital stay.

The presence of multiple hyperfunctioning glands and performance of inadequate initial parathyroidectomy lead to reoperations for recurrence. The potential benefit of using the QPTH assay intraoperatively is confirmation of adequate resection of hyperfunctioning parathyroid glands.

2. Intraoperative QPTH assay during parathyroidectomy

The clinical utility of QPTH assay in parathyroidectomy was first reported in 1988 in a study employing a modified iPTH IRMA assay [6]. Subsequently, the QPTH assay was improved by using radioactive [7-9] and non-radioactive [2,10,11] procedures, and the use of non-radioactive procedures allowed the quick assay to be performed in the operating room.

Combined preoperative localization of parathyroid tumors by sestamibi scintigraphy and intraoperative QPTH assay was first suggested by Irvin et al. [2] in 1993. The

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QPTH assay has a 10-min turnaround time and offers several advantages [12]. The operative failure rates have improved compared to parathyroidectomy without these surgical adjuncts, and the operative failure rate of initial parathyroidectomy in Irvin's institution has decreased significantly, from 6% to 1.5% [12]. The intraoperative use of the QPTH assay has been of help in reoperations after failed initial parathyroidectomy or late recurrence, and the success rate of reoperative parathyroidectomy has improved from 76% to 97% since the introduction of QPTH.

Most reports have confirmed the accuracy and utility of this approach [13]. The QPTH assay is usually performed by obtaining a baseline PTH level and then measuring the PTH levels 5, 10, and 15 min after resection of the putative hyperfunctioning parathyroid tissue. Since the half-life of intact PTH has been shown to be 3.5–4 min, if the intact PTH level decreases more than 50% below the preexcision level, the assay predicts postoperative normocalcemia [2]. A return to a calcium level of 10.2 mg/dl or less is considered a successful outcome. Weber and Ritchie [14] reported that intraoperative QPTH monitoring can accurately predict the outcome of parathyroid surgery in patients with solitary adenomas, but that this assay may underestimate the extent of resection required in patients with parathyroid hyperplasia. When compared to parathyroidectomies guided by the appearance of abnormal parathyroid gland morphologically, intraoperative QPTH assay accurately predicts the disease state in 89% of patients [15]. In addition to a shorter operating time and less associated morbidity, directed parathyroidectomy can also realize significant cost reductions. The intraoperative QPTH assay may be particularly useful in complicated cases and in patients undergoing a second operation. However, it does have some limitations and should not be used as a substitute for a thorough knowledge of the wide spectrum of potential findings that may be observed during operations for hyperparathyroidism [16].

Sokoll et al. [17] used QPTH assay in 195 patients and reported an overall accuracy of the assay in predicting surgical success of 88% using a 50% decrease at 5–10 min as the criterion, and of 97% when the subset of patients with delayed decreases of PTH was included. Agarwal, Delbridge, et al. used a decrease in QPTH to below 50% of the preoperative level and to within the normal range as the criteria for cure, and obtained the following results of QPTH in 88 patients: true positive in 78 patients, false negative in seven, false positive in one, and true negative in two [18]. They concluded that QPTH is an accurate test, although the false-negative and false-positive rates reduced its cost-effectiveness when used as part of an intraoperative decision analysis. Tonelli et al. [19] reported 16 cases of MEN type 1 treated by total parathyroidectomy with autotransplantation of parathyroid tissue in which the QPTH levels showed a stepwise decrease during surgery, reaching a mean value of 22.3% of the baseline 20 min after removal of the last gland, suggesting that it is a valuable adjunct for confirming complete cure of patients with multiglandular involvement.

Flentje et al. [20] reported that after removal of the adenoma, the PTH level fell to the normal range within 15 min, but that it did not decrease to the normal range following excision of the first parathyroid mass in any of the patients with multiglandular disease. Tonelli et al. [19] found that the total volume of the parathyroid glands correlated with the basal PTH level. These findings indicate that the pattern of the intraoperative PTH decrease is helpful in differentiating between uniglandular and multiglandular disease. However, in a retrospective study of 20 patients with double parathyroid adenomas treated by conventional parathyroidectomy with resection of two abnormal glands, Gauger et al. [21] reported QPTH levels in 11 of the 20 patients with false-positive results of 28% at 5 min and 18% at 10 min following resection of the first gland, and the false-positive QPTH rate was 55%. They suggested that caution be exercised when terminating limited parathyroidectomy based on a curative fall in QPTH levels. In patients with double parathyroid masses in which the volume of one parathyroid mass was greatly increased, and the other was only slightly increased, the PTH levels almost reached the normal range (decreased to more than 50% below the baseline) after removal of the larger mass, creating the impression that curative parathyroidectomy had been achieved. However, we think that curative resection is confirmed after parathyroidectomy when PTH levels decrease to within the normal range intraoperatively, and that curative resection is confirmed after total parathyroidectomy when the PTH levels become undetectable intraoperatively.

Clary et al. [22] reported that all 13 patients with renal hyperparathyroidism had significant decreases in PTH levels after parathyroidectomy (mean 84.%), but the long-term follow-up and larger numbers of patients will be crucial in defining the role of QPTH monitoring during parathyroidectomy for renal hyperparathyroidism. The intraoperative decrease in PTH in patients with renal hyperparathyroidism is reproducible but much slower than in patients with normal renal function [23] because of the longer half-life of intact PTH in renal failure (6.6 vs. 2.2 min) [24]. The PTH levels in patients with renal hyperparathyroidism are characteristic of the patient-to-patient variability of the half-life of PTH [24] and its molecular heterogeneity and biphasic metabolism [23]. The QPTH in renal hyperparathyroidism is useful as an indicator of adequate resection of the hyperfunctioning parathyroid gland and the presence of supernumerary glands [23]. Lokey, Proye et al. reported that a decrease of more than 50% of the baseline by 20 min after resection is predictive of cure, while a decrease of less than 40% suggests a missed or hyperfunctioning supernumerary gland and is predictive of failure [23].

Use of the QPTH assay will make both patient and surgeon even more comfortable with minimally invasive parathyroidectomy or adenomectomy (e.g., limited, direct mini-incision, targeted, focused, focal, concise procedures), video-assisted parathyroidectomy [3,25], and endoscopic parathyroidectomy [26,27]. The QPTH assay avoids the need for bilateral or unilateral exploration and identification of all parathyroid glands [3,25]. This results in reduced operation time, limiting the cost of the procedure. Frozen sections are not useful and do not provide any additional information when the QPTH assay is used. Udelsman [28] reported performing 401 procedures by standard parathyroidectomy and that 255 patients were selected for minimally invasive parathyroidectomy. The success rate for the entire series was 98%, with no significant differences between the two groups, and the overall complication rate of 2.3% reflected a 3.0% rate and 1.2% rate in the standard group and minimally invasive parathyroidectomy group, respectively, indicating that minimally invasive parathyroidectomy has replaced traditional exploration for most patients. Perrier, Clark, et al. reported that their collected data showed that use of preoperative sestamibi scintigraphy and intraoperative QPTH assays enabled focused parathyroidectomy in 64% of the patients, with an acceptable 93% success rate, in contrast to a 98% success rate with bilateral exploration, including all patients with sporadic primary hyperparathyroidectomy [29]. Bilateral exploration remains the treatment of choice for patients with familial primary hyperparathyroidism, secondary and tertiary hyperparathyroidism and coexisting thyroid pathology, equivocal or negative sestamibi scintigrams, or scintigrams suggesting multiple glands, because the success rate with QPTH would only be approximately 63%. In a large series of patients, Miccoli et al. [3] reported that minimally invasive video-assisted parathyroidectomy offered better cosmetic results and less postoperative discomfort at similar costs compared with traditional parathyroidectomy.

3. Initial experience with intraoperative QPTH assay during minimally invasive parathyroidectomy

In a series of 39 consecutive patients with primary and renal hyperparathyroidism treated by minimally invasive parathyroidectomy, there were 30 patients with primary hyperparathyroidism (26 single adenomas, two double adenomas, one MEN type1, one double parathyroid carcinoma, one supernumerary adenoma), consisting of 12 males and 18 females, and their median age was 54 years. Surgery in 26 patients was by direct mini-incision (2-cm) parathyroidectomy, and in four patients by endoscopic parathyroidectomy via the anterior chest. The 13 renal hyperparathyroidism patients consisted of five males and eight females, and their median age was 59 years. Surgery in all patients consisted of direct mini-incision (3-cm) total parathyroidectomy and autotransplantation of parathyroid tissue. Both ultrasonography and sestamibi scintigraphy were routinely performed preoperatively. Exclusion criteria were unsatisfactory parathyroid localization, multinodular goiter, irradiation of the neck, suspicion of malignancy, and "social" circumstances.

Blood samples for QPTH assay were drawn from a peripheral vein immediately before the skin incision, 5, 10, 15, and 45 min after excision of the first enlarged parathyroid gland in the patients with primary hyperparathyroidism, and after excision of the final enlarged parathyroid gland in the patients with renal hyperparathyroidism. PTH was analyzed by the Nichols Institute Diagnostics QuiCK-Intraoperative Intact PTH Assay, an immunochemiluminometric assay (ICMA) [2,4].

Direct mini-incision parathyroidectomy was performed through a 2-cm-long transverse incision along the medial border of the sternocleidomastoid muscle for adenomectomy, and a 3-cm-long transverse incision in the midline of the anterior neck for total parathyroidectomy. The sternocleidomastoid muscle was retracted laterally, and the thyroid was drawn medially, allowing the surgeon to reach the loose areolar tissue of the tracheoesophageal groove. After identifying the enlarged gland, it was excised, and its feeder vessels were ligated. The surgical procedures of endoscopic parathyroidectomy are described elsewhere [26,27].

The PTH levels and percentage changes in PTH from baseline in the 26 primary hyperparathyroid patients with single adenomas and a 50% decline in PTH after gland excision are shown in Figs. 1 and 2. The mean baseline PTH level in the 26 patients with single adenomas was 306.8 ± 289.5 pg/ml, and the mean 5-min PTH level after resection of the enlarged parathyroid gland in these patients was 72.8 ± 59.4 pg/ml, representing a mean drop of 76.2%. A 50% decrease in PTH level at 5 and 10 min after resection of an enlarged parathyroid gland was found in 84.6% and 96.2%, respectively, of the 26 patients, and the PTH levels returned to within the normal range by 15 min after resection of the enlarged parathyroid gland in 20 of them (76.8%). One patient had a history of MEN type1 (Fig. 3), and the intraoperative PTH levels during parathyroidectomy showed a stepwise decrease, falling to within normal limits (21.6 pg/ml) by 5 min after excision of the fourth gland. One patient had double parathyroid carcinomas. Two parathyroid masses were localized by sestamibi scintigraphy and ultrasonography preoperatively. The PTH level had decreased to 56.2% of the baseline by 5 min after resection of the left upper parathyroid mass, but it had not reached 50% of the baseline (Fig. 4). Right hemithyroidectomy was then performed to remove a parathyroid mass embedded in the right thyroid gland, and the PTH level decreased, falling to the normal range by 15 min after removal of the second

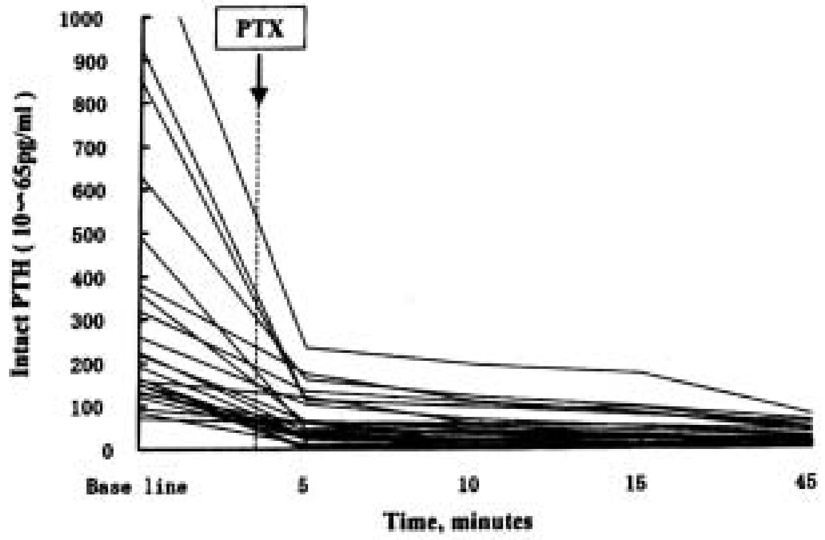

Fig. 1. PTH levels of 26 primary hyperparathyroid patients with single adenomas.

parathyroid mass. Both parathyroid masses showed complete capsular invasion and tumor infiltration of the thyroid gland (right parathyroid mass) microscopically, indicating a parathyroid carcinoma.

The mean baseline PTH level of the 13 patients with renal hyperparathyroidism was 847.1 ± 695.6 pg/ml (Fig. 5). After total parathyroidectomy, the mean 5-min PTH level was 188.2 ± 110.6 pg/ml, representing a 58.8% decrease from the baseline, and 50% decreases in PTH levels at 5, 10, and 15 min after total parathyroidectomy were found in 77.5%, 92.3%, and 92.3% of the 13 patients, respectively (Figs. 5 and 6). The PTH levels returned to the normal range in three of the 13 patients (23.1%) by 15 min after total parathyroidectomy. The percentage change in PTH from baseline in renal hyperparathyroidism was less than in primary hyperparathyroidism.

The QPTH assay yielded excellent results and predicted the success of parathyroidectomy, but it must be combined with other information derived from preoperative informa-

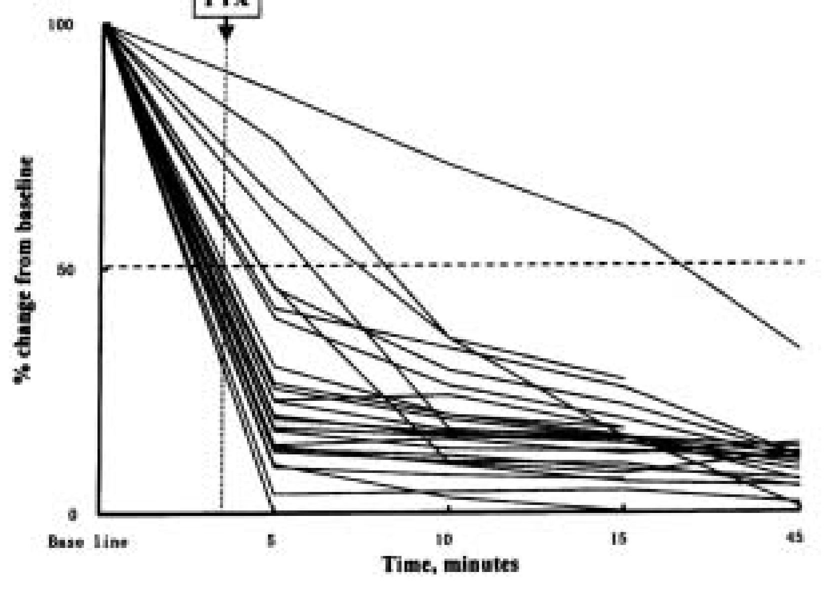

Fig. 2. Percentage change in PTH from baseline in patients with single adenomas.

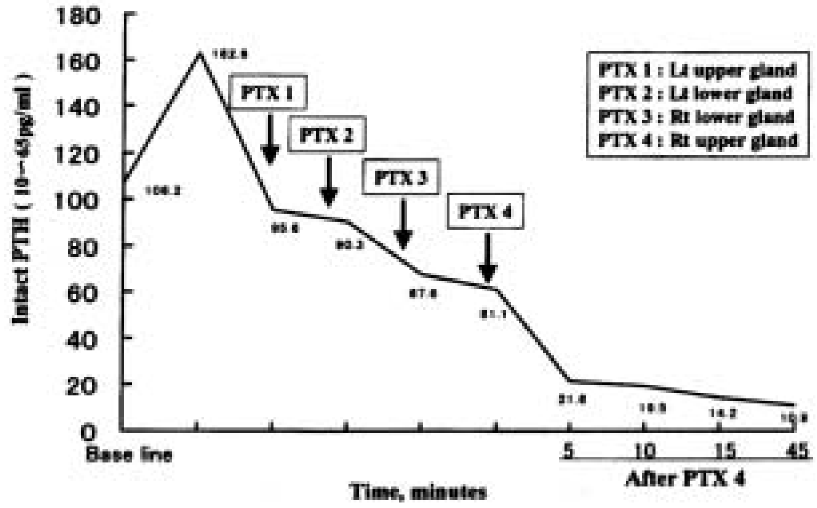

Fig. 3. Change in PTH level in a patient with MEN type1.

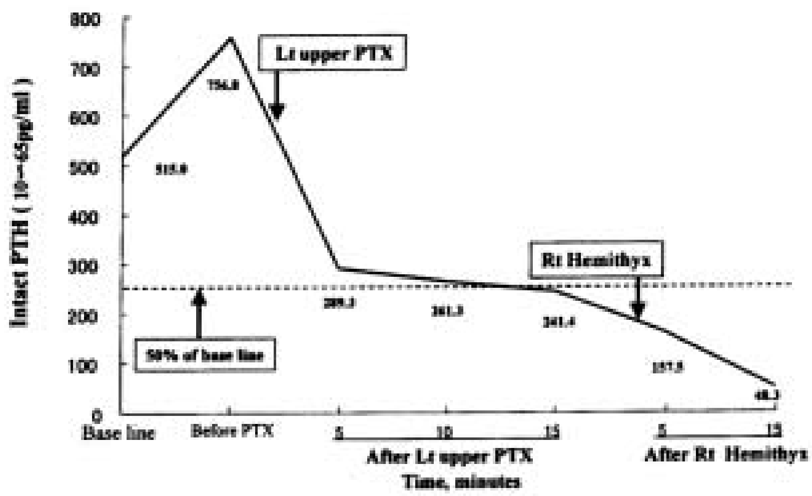

Fig. 4. Change in PTH level in a patient with double parathyroid carcinomas.

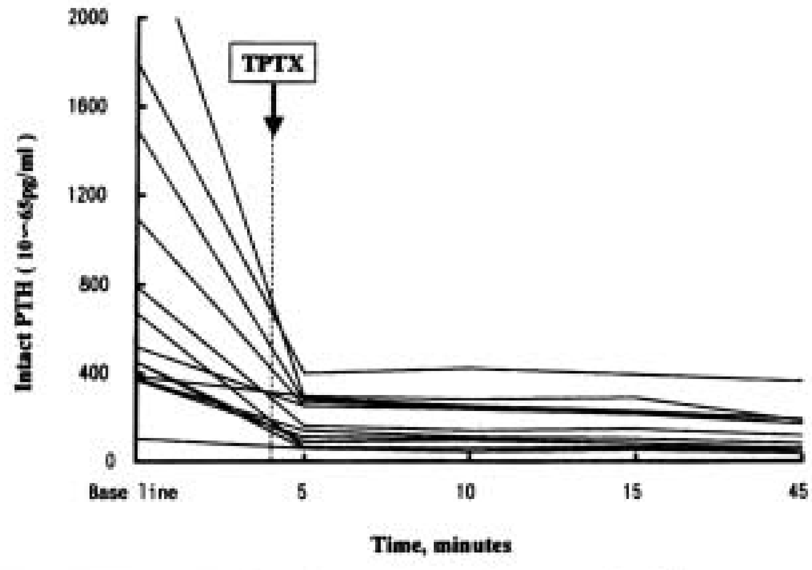

Fig. 5. PTH levels in 13 patients with renal hyperparathyroidism.

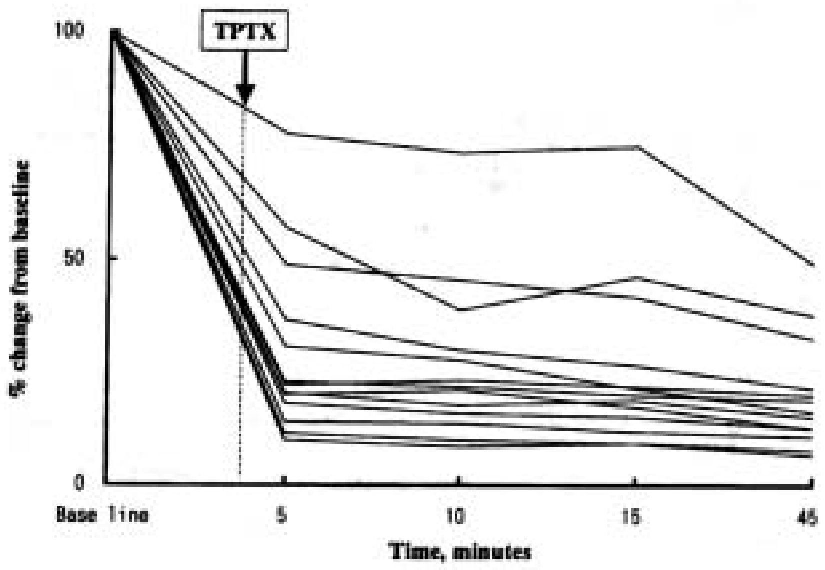

Fig. 6. Percentage change in PTH from baseline in patients with renal hyperparathyroidism.

tion and direct observation to maximize the success of surgical intervention. Further studies will be necessary to evaluate the possible risk of recurrent or persistent hyperparathyroidism in cases of false-positive results.

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