Recent Advances in the Management of Primary Hyperparathyroidism

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Key words: Hyperparathyroidism, Minimally invasive parathyroidectomy, Endoscopic parathyroidectomy, Quick intact PTH assay, Percutaneous ethanol injection therapy

Introduction

PRIMARY hyperparathyroidism (PHPT), a common cause of hypercalcemia due to excessive secretion of PTH, is usually associated with hypophosphatemia and elevated serum chloride levels. PHPT was often complicated by nephrolithiasis and osteitis fibrosa in the past, but routine screening of serum Ca and the development of the intact PTH assay have contributed to earlier detection of PHPT [1]. The pathophysiology of PHPT is related to the loss of the suppressive effect of extracellular Ca on PTH secretion, and the loss of normal sensitivity to Ca in parathyroid adenoma is associated with a reduction in the number of Ca-sensing receptors.

There are many causes of PHPT, and optimal therapy must be individualized for each patient according to this etiology [2]: 1) solitary adenoma (85%); 2) multigland hyperplasia (10%), which may occur sporadically or in association with multiple endocrine neoplasia (MEN) type 1 or 2; 3) double adenoma (3%); and 4) carcinoma (2%).

The serum Ca level usually shows mild elevation in as much as 60% of the PHPT patients, who exhibit no signs or symptoms [2]. Improvement of PTH assays, however, has permitted accurate early diagnosis of PHPT, and asymptomatic PHPT and normocalcemic PHPT must be adequately treated.

PHPT patients tend to have a greater reduction in bone mineral density in cortical bone, and some postmenopausal women with PHPT exhibit a marked reduction of bone mineral density in the lumbar spine [2]. Some PHPT patients appear to be at increased risk for progression or complications of PHPT. If PHPT is complicated by vitamin D deficiency, the strong biochemical drive to convert 25-hydroxyvitamin D to 1,25 (OH) 2D may make PHPT more active by worsening the vitamin D deficiency and thereby accelerate the progression of PHPT [3].

The prevalence of PHPT is about 0.1% of the United States population, and it appears to be far lower in the Japanese population [1]. Nevertheless, we believe that Japanese endocrinologists, urologists, and endocrine surgeons are not sufficiently aware of PHPT and require greater clinical knowledge about it.

The best surgical strategy enables PHPT to be resolved while minimizing such complications [4] as persistent hyperparathyroidism, recurrent hyperparathyroidism, postoperative hypoparathyroidism, and recurrent laryngeal nerve palsy. The surgical strategy must also make efficient use of operative time and resources. The success rate for parathyroidectomy performed by experienced endocrine surgeons is 95% or better [5]. Persistent hyperparathyroidism is usually the result of missing either an ectopic tumor or one of multiple abnormal glands. Recurrent hyperparathyroidism usually occurs in patients with familial disease, such as familial isolated hyperparathyroidism and MEN 1. Until recently, there was controversy as to whether unilateral or bilateral neck exploration was preferable for primary hyperparathyroidism.

Innovations such as the intraoperative quick intact
PTH assay and Tc-99m sestamibi (MIBI) scintigraphy have allowed the development of radioguided parathyroidectomy, which is minimally invasive and precise. 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.

**Medical Management of PHPT**

The lack of progression makes medical management a reasonable means of treating asymptomatic PHPT and normocalcemic PHPT [1]. Administration of bone antiresorbers, estrogen, and estrogen-progesterone is useful for improving bone mineral density and biochemical indices in postmenopausal women [1], while the long-term efficacy of calcitonin and bisphosphonate therapy in such patients is unclear [6]. Other promising drugs for the treatment of PHPT are the Ca-sensing receptor agonists, calcimimetics [7]. These new drugs reduce PTH secretion directly via extracellular Ca-sensing receptors in parathyroid chief cells.

At least in asymptomatic PHPT and normocalcemic PHPT patients who are not at risk for greater morbidity or mortality, parathyroidectomy and medical management with bone antiresorbers provide a useful means of increasing bone mineral density when bone mineral loss is detected [8].

**Effect of Parathyroidectomy in Patients with PHPT**

Parathyroidectomy is the single and most effective treatment option for PHPT. The NIH Consensus Development Conference provided guidelines for the management of asymptomatic PHPT in 1990 [9], and the need for prospective studies of the clinical features of PHPT and its surgical and non-surgical treatment regimens was underscored. Adherence to the recommendations in the guidelines was analyzed in 1998, and the criteria for parathyroidectomy were found to vary widely even among highly experienced surgeons [10]. Mollerup et al. [11] reported the risk of renal stone episodes and risk factors for renal stones in 674 patients with PHPT before and after parathyroidectomy by controlled retrospective follow up study. PHPT is associated with increased risk of renal stones more than 10 years before the diagnosis is established. Parathyroidectomy is associated with an 8.3% risk reduction in renal stone events, and more than 10 years after parathyroidectomy the risk returns to frequency of controls. Male sex, younger age, and previous stone events are associated with a greater risk of stone disease. As for bone disease, the long-term effects of PHPT, whether treated or untreated, on bone density and fracture risk are not clear. Rao et al. [12] followed the course of forearm bone mineral/bone width and Z-scores in 108 patients who underwent successful parathyroidectomy and 108 who remained unoperated. They concluded that cessation of further bone loss consequent to successful parathyroidectomy would eventually lead to abatement of the excess fracture risk, but the actual benefit to individual patients will depend mainly on their remaining life expectancy. Vestergaard et al. [13] studied fracture risk in 1201 patients with newly diagnosed PHPT, and found no differences in fracture risk between those who had and those did not have parathyroidectomy, taking age, and previous fractures into account. Cardiovascular disease (atherosclerosis and subsequent myocardial infarction) has been associated with primary hyperparathyroidism. Vestergaard et al. [14] studied cardiovascular events in a total of 674 patients who underwent parathyroidectomy and 2021 age- and gender-matched controls. They concluded that there was an increase in acute myocardial infarction up to 10 years prior to surgery. The risk of myocardial infarction decreased to a normal level after surgery, which may be important for preventing cardiovascular disease in patients with PHPT. However, controversy regarding the management of mild PHPT continues, but we think that parathyroidectomy should be recommended for all patients with hypercalcemia and PHPT. The recent development of minimally invasive parathyroidectomy under sedation and local anesthesia decreases the likelihood of many potential problems, even in patients with mild hypercalcemia and no apparent symptoms.

**Conventional Parathyroidectomy**

The success of bilateral neck exploration with or without biopsy of normal-appearing glands depends on the surgeon’s ability to differentiate between normal
and abnormal glands on the basis of size. In experienced hands, this approach results in a 90% to 98% success rate with low morbidity [10]. Some surgeons have performed unilateral neck exploration when only one enlarged gland and an ipsilateral gland of normal size were found [15], and experienced endocrine surgeons have reported excellent results using this limited surgical approach. In the 1990s, the availability of MIBI and ultrasonography (US) greatly facilitated surgical policies regarding unilateral neck exploration [16–18], and in 1995 and 1996 the author performed unilateral neck exploration in all 33 of his patients with solitary parathyroid adenoma [19]. Double-phase MIBI-99m Tc subtraction scintigraphy, alone or with SPECT, was performed in combination with US in each case [17] and the sensitivity of the MIBI scintigraphy and US was 92% and 86%, respectively. All of the patients were treated successfully using a unilateral approach except for the two patients in whom a solitary adenoma was detected in the mediastinum (Fig. 1). The average operating time, excluding the two cases requiring a mediastinectomy, was 41 min. No complications occurred in any of the patients. Although the surgical success rate is influenced by the length of the follow-up period, the success rate in this group to date has been 100%. Thanks to techniques that allow proper localization, the unilateral approach for patients with primary hyperparathyroidism is less invasive, associated with fewer complications, and can be tolerated by most patients with primary hyperparathyroidism [20]. Unilateral exploration under local anesthesia is a useful method of treatment for patients at high risk, such as those with respiratory or cardiovascular diseases. A retrospective study found no differences in surgical outcome between unilateral exploration and bilateral exploration [4]. It could therefore be argued that unilateral exploration is, at the very least, not less successful than bilateral exploration. However, no prospective, controlled study has ever been performed, the arguments for and against unilateral neck exploration are mainly theoretical.

**Minimally Invasive Parathyroidectomy**

MIBI scintigraphy is a new technique that enables...
accurate localization of parathyroid adenomas, and a new procedure known as radio-guided parathyroidectomy has been developed using this modality [21]. Combination of this procedure with the intraoperative quick intact PTH assay, which provides biochemical confirmation that the adenomas have been completely excised, could revolutionize the new procedure for parathyroidectomy [22]. In addition, the development of endoscopic parathyroidectomy has also been a revolutionary advance in surgical procedures for parathyroidectomy [23].

Irvin et al. [22] developed a quick intraoperative assay for determining intact PTH levels, and it is claimed to prevent failure during parathyroidectomy for hyperparathyroidism [24]. The causes of operative failure have included multiglandular disease, ectopic parathyroid glands, supernumerary parathyroid glands, errors in frozen section evaluations, and misdiagnosis. The intraoperative quick intact PTH assay is recognized as a useful method of determining whether all hyperfunctioning tissue has been completely excised. The intraoperative intact PTH assay is usually performed by obtaining a baseline PTH level and then measuring PTH level 5 and 10 min after resection of the putative hyperfunctioning parathyroid tissue. The interval between drawing the blood sample and obtaining the measurement data is 10 min. Since the half-life of intact PTH has been shown to be 3.5–4 min, if the intact PTH level decreases to more than 50% below the pre-excision level, the assay predicts postoperative normocalcemia [25]. A return to a calcium level of 10.2 mg/dl or less is considered a successful outcome. Weber et al. [26] reported that intraoperative PTH monitoring can accurately predict the outcome of parathyroid surgery in patients with solitary adenomas, but that the assay may underestimate the extent of resection required in patients with parathyroid hyperplasia. The intraoperative PTH assay may be particularly useful in complicated cases and in patients undergoing a second operation. The assay does, however, have some limitations and should not be used as a substitute for a thorough knowledge of the wide spectrum of potential findings that can occur during operations for hyperparathyroidism [27]. Because false-positive results are sometimes obtained, it will be necessary to conduct further study to evaluate the risk.

We have treated 45 consecutive patients with PHPT or renal hyperparathyroidism using intraoperative PTH assay as of March 2002 [24]. There were 31 patients with PHPT (29 single adenomas, one MEN type 1, one double parathyroid carcinomas). The length of the skin incision was 2 cm in patients with a single adenoma and 3 cm in patients with multiglandular disease. The 14 renal hyperparathyroidism patients were treated by mini-incision open total parathyroidectomy (3 cm) and autotransplantation of parathyroid tissue. The mean baseline PTH level in the 29 patients with single adenomas was 321 ± 295 pg/ml, and the mean 5-min PTH level after resection of the enlarged parathyroid gland in these patients was 70 ± 61 pg/ml, representing a mean drop of 78%. A 50% decrease in PTH level at 5 and 10 min after resection of an enlarged parathyroid gland was found in 86% and 100%, respectively, of the 29 patients, and the PTH levels returned to within the normal range by 15 min after resection of the enlarged parathyroid gland in all of them (100%) (Fig. 2). Among the 14 patients with renal hyperparathyroidism, 50% decreases in PTH levels at 5, 10, and 15 min after total parathyroidectomy were found in 76%, 91%, and 93%, respectively. In four (29%) of the 14 patients, the PTH levels returned to within the normal range by 15 min after the total parathyroidectomy.

The intraoperative decrease in PTH in patients with renal hyperparathyroidism is reproducible but much slower than in patients with normal renal function [28] because of the longer half-life of intact PTH in renal dysfunction (6.6 vs. 2.2 min) [29]. The PTH levels in patients with renal hyperparathyroidism are characteristic of the patient-to-patient variability of the half-life of PTH.

Most commercial intact PTH assays cross-react with non-(1-84) PTH, a PTH fragment with hydrophobicity similar to that of synthetic 7-84 PTH [30]. Subsequent studies have shown that the non-(1-84) PTH fragment is amino-terminally truncated and has a highly potent inactivating effect on 1-84 PTH function. The proportion of non-(1-84) PTH in patients varies over a much wider range, usually accounting for 20% to 60% of the immunoreactivity in samples obtained from hyperparathyroid patients [31]. A cyclase activating PTH (CAP) measured by a novel immunoradiometric (IRMA) assay was recently developed to specifically measure 1-84 PTH exclusively [32]. Yamashita et al. found that the plasma CAP value decreased more rapidly than intact PTH after parathyroidectomy, depending on the amount of 7-84 PTH in circulation, and concluded that the CAP assay may be a more useful
adjunct to parathyroidectomy than the currently used intact PTH assay [31].

The recent development of radioguided parathyroidectomy has allowed parathyroidectomy to be performed quickly by a significantly less invasive procedure [21]. Murphy and Norman found that lymph nodes, normal parathyroid glands, and adipose tissue never contained more than 2.2% of background radioactivity, whereas thyroid and hyperplastic parathyroids contained 5.5% and 7.5%, respectively, but never more than 16% [21]. By contrast, parathyroid adenomas were found to contain 59% of background activity, with a range of 18–136%, and any excised tissue containing more than 20% of background radioactivity was confirmed to be a solitary parathyroid adenoma (the 20% rule). Their study showed that radioguided parathyroidectomy was successful in 97% of patients, and that parathyroid adenomas contained more than 20% of the background activity. However, one of the major limitations of this procedure is related to the presence of thyroid nodules [33]. Thyroid nodules and thyroiditis can accumulate MIBI and therefore result in false-positive foci. Denham and Norman found that radioguided parathyroidectomy is less expensive than the standard operation because of the shorter operating room and recovery room time, shorter hospital stay, and smaller number of frozen sections taken [34]. Bonjer et al., on the other hand, reported similar rates of success and complications in patients treated by probe-guided surgery and conventional surgery, and concluded that despite the MIBI probe appearing to be a valuable tool in parathyroid surgery, its use does not improve the outcome of surgery [35]. Reoperative parathyroid surgery is associated with a complication rate several fold higher than that of first-time operations for the same disease. Radioguided parathyroidectomy is extremely effective in patients with recurrent or persistent hyperparathyroidism, who have undergone previous neck exploration for parathyroid and thyroid disease.

We have treated 21 patients with PHPT by minimally invasive radioguided parathyroidectomy [36]. A 20 mCi dose of MIBI was injected 90–120 min before the operation, and the gamma probe with tiny tip was applied to the incised wound. Single adenomas or abnormal glands were identified correctly by a MIBI scintigram in 18 of 19 patients, and by the gamma probe in 17 of the 19 patients. In the two patients with multiple parathyroid masses, three of the four masses were identified on MIBI scintigrams, and two of them were identified with the gamma probe. The hypercalcemia was corrected in all 21 patients.

Radioguidance was used much more selectively as experience accumulated, and radioguided parathyroidectomy is currently indicated for sporadic PHPT in patients with deep, retroesophageal lesions, ectopic glands, or persistent or recurrent PHPT [36, 37].

During the last five years several minimally inva-
sive parathyroidectomy procedures have been developed for the treatment of PHPT, ranging from a pure endoscopic approach (completely closed technique) [38, 39] characterized by constant gas insufflation, to video-assisted gasless techniques [40] and minimally invasive open parathyroidectomies guided either by intraoperative quick PTH assay [41], intraoperative radioisotopes [21] or preoperative localization studies [42]. The procedure we have described can be classified as a minimal-access surgery, and it provides both a better scar cosmetically and a less painful postoperative course. Its disadvantages include a longer operating time and the possible risk of missing multi-glandular disease. Initial reports on endoscopic and video-assisted unilateral parathyroidectomy state that the procedures are useful in cases of localized single-gland disease with no evidence of nodular goiter or history of prior neck exploration [42]. Thus, endoscopic and video-assisted techniques are highly feasible. Inaccurate localization, larger parathyroid adenomas, nodular goiter, or prior thyroid surgery complicate or eliminate the usefulness of these new techniques. Our successful use of endoscopic parathyroidectomy with gas insufflation for bilateral parathyroidectomy and subtotal thyroidectomy led us to reconsider our strategy for operating on thyroid lesions and multiple parathyroid masses [43]. As a result, we developed a new technique involving the performance of endoscopic parathyroidectomy via an axillary and anterior chest approach, with no scarring of the neck. In this approach, three trocars are inserted via the axilla or anterior chest, thereby completely avoiding neck incisions [39]. Hypesthesia and paresthesia of the neck are also negligible because of the small subplatysmal space.

Minimally invasive open parathyroidectomy seems to be suitable for patients with PHPT [44, 45]. Our procedure is performed through a 2-cm mini skin incision and differs from the conventional procedure in requiring a smaller skin incision and no raising of a skin flap. The skin incision is made just inside the anterior border of sternocleidomastoid muscle (lateral approach) or in the midline of the anterior neck. The lateral approach is associated with a less hypertrophic scar and fewer patient complaints of unpleasant sensations or discomfort on swallowing. The small skin incision and small working space result in a good cosmetic outcome and less invasiveness. The mini-incision open procedure is thought to be the least invasive of all parathyroidectomy procedures.

Parathyroid malposition is discovered in several percent to more than 10% of patients with PHPT, and incidences of an ectopic parathyroid mass in the mediastinum of 1.0%–2.2% have been reported [46]. Invasive procedures, such as median sternotomy, thoracotomy, and rib resection, have been employed to surgically treat such mediastinal parathyroid masses, and the development of video-assisted thoracic surgery (VATS) instrumentation and refinements of endoscopic surgical techniques have allowed increasing applications of VATS to ectopic mediastinal parathyroid masses (Fig. 3). The introduction of MIBI scintigraphy has made it possible to identify ectopic parathyroid masses with a high degree of accuracy. To perform VATS, three to four trocars are inserted between the fourth and seventh ribs via a lateral approach, and the masses are identified based on the diagnostic imaging, and excised by the shortest possible route. The effectiveness of the technique for intraoperatively identifying parathyroid lesions has been well documented since Norman and Denham introduced radioisotope navigation using MIBI for video-assisted thoracic parathyroidectomy [47].

**Percutaneous Ethanol Injection Therapy (PEIT)**

Ultrasonographic examination of the neck is performed with a color-Doppler ultrasonograph and a
7.5 MHz transducer [48], and the ethanol injections were performed on an outpatient basis. Under direct real-time ultrasonographic guidance (B mode), the PEIT needle is inserted into the parathyroid glands and ethanol is injected while monitoring Doppler blood flow mapping.

Reports in the literature vary with regard to the efficacy of this procedure [49]. Karstrup postulated that recurrence indicates incomplete necrosis, with survival and regrowth of functioning cells [50]. Kakuta et al. described PEIT as seeming to be more effective for treatment of PHPT secondary to solitary adenoma [48]. The function of the causative gland in patients with PHPT must be completely eliminated. PEIT is currently indicated in poor risk patients, when reoperation is considered technically unsafe, and the patient prefer it.

Conclusion

The development of high-resolution ultrasonography, MIBI scintigraphy, radioguided surgery, and intraoperative quick intact PTH assay has been paralleled by the introduction of several minimally invasive parathyroidectomy procedures that have come into widespread use for the treatment of PHPT.

The new minimally invasive technique described above is expected to lead to improved patient comfort, shorter hospital stay, and favorable cosmetic results in a select group of patients, as well as being an this operative procedure that may be performed on an outpatient basis.

References


