Surgical Management Strategies in Patients with Primary Hyperparathyroidism: Which Technique in Which Patients?

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Key Words

Primary hyperparathyroidism · Hypercalcemia · Surgery · Unilateral neck exploration · Bilateral neck exploration · Sestamibi scintigraphy

Abstract

Objective: This study was planned to investigate the efficacy of either ^{99m}Tc-sestamibi scan or ultrasonography in predicting the operative treatment in patients with primary hyperparathyroidism (PHPT). **Subjects and Method:** Thirty patients (25 female, 5 male; mean age: 53 years) being operated for symptomatic primary PHPT were included in this study. Ultrasonography was used in 29 patients while ^{99m}Tc-sestamibi scintigraphy was done in 28 patients to localize the hyperfunctioning gland(s). Standard bilateral neck exploration was done in 6 patients. Although unilateral intervention had been planned for 24 patients, bilateral intervention was performed in 9 of them. **Results:** Sensitivity of ^{99m}Tc-sestamibi was 81%, while that of ultrasonography was 42%. ^{99m}Tc-sestamibi localization method led to misleading results in 10/28 (35.7%) patients. False-positive localization and accompanying thyroid pathologies played an important role in determining transition from unilateral

to bilateral intervention. **Conclusion:** Our findings indicate that bilateral intervention remains a successful management option without prior localization in patients with PHPT especially in an endemic goiter region.

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Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by abnormal parathormone (PTH) release and hypercalcemia [1]. PHPT is the most common etiological factor for hypercalcemia with a prevalence of 0.1–0.5% [2–5]. Its expected incidence is 1 in 1,000 male and 2–3 in 1,000 female subjects [6]. The disease affects postmenopausal women, peaking in the 5th and 6th decades. Its male:female ratio is 1:3 [7].

The definitive treatment of symptomatic patients is the extraction of the abnormal gland(s). Currently, it is possible to find asymptomatic cases through routine measurement of serum calcium using multichannel serum analyzers [8]. Half of the asymptomatic cases can be detected without surgical intervention. NIH consensus conference determined the indications for surgery [9].

Bilateral neck operation, defined as finding the four glands and extracting the hyperfunctioning ones, is the accepted gold standard in surgical treatment of PHPT [10]. Nowadays, the idea of surgical intervention to remove only the abnormal gland is becoming important due to the abundance of nonsurgical localization methods. Scintigraphy, ultrasonography (US) and intraoperative nuclear scanning methods can be used for localization. However, there is controversy about the methods and their diagnostic values. Unilateral neck exploration together with a localization method is usually sufficient to cure adenoma-related disease in 80–90% of the cases [11–13]. Latest reports have provided evidence diminishing the importance of nonsurgical localization methods [14, 15]. Equally the probability of multiple gland disease cannot be excluded.

Hence, we decided to investigate the efficacy of either ^{99m}Tc -sestamibi scintigraphy or US in predicting surgical treatment for patients with PHPT.

Subjects and Methods

Thirty patients operated for PHPT were included in the study. Data were collected through a prospectively maintained longitudinal database along with retrospective chart review. Informed consent was obtained from all the patients according to the criteria of our Institutional Human Subject Research Committee. The diagnosis of PHPT was based on the following criteria: calcium levels >10.5 mg/dl, intact PTH levels >65 pg/ml, increase in urinary calcium excretion, decrease in serum phosphorus levels and excluding past history of familial hypocalciuric hypercalcemia or lithium administration. All the patients were symptomatic.

US (Toshiba Power Vision 6000 5–7.5 mega prob, Japan) was performed in 29 patients while technetium- 99m methoxyisobutylisonitrile (^{99m}Tc -sestamibi) scintigraphy was available in 28. Dynamic and static images were acquired after administration of 740 MBq (20 mCi) ^{99m}Tc -sestamibi using a pinhole camera (MG 11 Orbiter, M1G), dynamic images (15 per minute) in 128×128 matrices, and static image was acquired 2 h later. The results were expressed as true positive when the enlarged gland was conveniently localized during operation.

ILab 1800 autoanalyzer (Lexington, USA) was used to determine renal function, calcium, phosphorus and alkaline phosphates pre- and postoperatively in the patients. Intact PTH measurements were performed by using an automated analyzer device (Immulite, Diagnostic Products, Los Angeles, Calif., USA). Daily urinary calcium excretions were recorded from 24-hour urinary samples.

If a hyperfunctioning parathyroid gland was localized, unilateral intervention was performed. During intervention, when a large gland representing large adenoma by gross appearance was found, it was surgically extracted and sent for histopathological confirmation. If the indicated gland was normal in size, ipsilateral and contralateral parathyroid glands were explored sequentially. Subtotal parathyroidectomy was performed if all parathyroid glands were

Table 1. Symptoms and signs of patients with PHPT

Symptom/sign	n	%
Exhaustion	23	76.6
Muscle weakness	22	73.3
Bone pain	12	40.0
Dyspeptic complaints	26	86.6
Polyuria, polydipsia	11	36.6
Bone fracture	5	16.6
Brown tumor	7	23.3
Nephrolithiasis	13	43.3
Hypertension	14	48.2

larger than normal size, macroscopically suggesting hyperplasia. Bilateral intervention was done if the parathyroid gland was not localized or in patients with accompanying thyroid pathologies. If four parathyroid glands on each side were seen in bilateral exploration, the biggest one was extracted and sent to frozen section for confirmation. The decision to stop surgical exploration was based on the macroscopic appearances of glands.

Patients with accompanying thyroid disease also received intervention for the extra pathologies. Patients showing thyroid nodule preoperatively were also investigated for malignancy.

The patients were followed up for postoperative complications and hypocalcemia. Preoperative and intraoperative localizations were compared by means of diagnostic sensitivities. Patients having bilateral intervention were compared with respect to hospitalization periods and development of complications.

The results were expressed as mean $\pm$ standard error. The formula $[\text{true positives}/(\text{true positives} + \text{false negatives})] \times 100$ was used to determine the diagnostic sensitivities of scintigraphy and US. True positives were defined as patients whose localization and surgical findings were congruent, and false negatives were defined as patients having negative localization before surgery, but parathyroidal pathology was found intraoperatively; t test was used for statistical analysis with a value of $p < 0.05$ accepted as significant.

Results

Clinical and Laboratory Findings

Twenty-five patients were female (83.3%) and 5 were male (16.6%) with an average age of 53 (28–73 years). Nodular goiter was found in 11 of the patients by physical examination. Subperiosteal bone resorption and salt-paper appearance were found in direct graphics in 11 patients and brown tumors were observed in 7 patients. Symptoms and signs of the patients are shown in table 1. None of the patients had hypoalbuminemia. Mean serum absolute calcium concentration was 11.3 ± 0.8 mg/dl

(8.4–10.2 mg/dl); phosphorus 2.5 ± 0.8 mg/dl (2.7–4.5 mg/dl); intact PTH 437.7 ± 484.6 pg/ml (7–53 pg/ml); alkaline phosphates 356.2 ± 558.1 U/l (42–141 U/l), and 24-hour urinary excretion of calcium 428.0 ± 185.1 mg/day (<250 mg/day).

Localization Studies

For ^{99m}Tc -sestamibi scintigraphy in the 28 patients, the true-positive, false-positive and false-negative cases were 18, 6 and 4, respectively. In true-positive cases, the adenomas were localized at the right inferior in 9, left inferior in 7 and right superior in 2. Diagnostic sensitivity of ^{99m}Tc -sestamibi scintigraphy was 81%. In case of US, in the 29 patients, true-positive, false-positive and false-negative were in 11, 3 and 15 cases, respectively. The sensitivity of the technique was 42%.

Surgical Findings

Of the 30 patients, 15 each had bilateral or unilateral intervention, although unilateral intervention had been planned for 24 patients preoperatively, but it became necessary to do bilateral intervention in 9. Of the 9 patients with negative ^{99m}Tc scintigraphy, 6 had bilateral intervention. Parathyroid hyperplasia was found in 2/6. In 1/6 patients, although ^{99m}Tc -sestamibi scintigraphy demonstrated an adenoma in the right inferior, the indicated lesion was not found during bilateral interventions. Elevated serum calcium levels persisted after operation in this patient. Subsequently, the parathyroid adenoma was found in the mediastinum by radio-guided gamma probe in the second operation and postoperative serum calcium levels of this patient returned to normal. Adenoma was found in another localization in the remaining 3/6 patients. In addition, 3/9 patients had bilateral thyroidal nodular disease. Bilateral intervention was initially planned in 6 patients, because of negative (4/6) or lacking scintigraphy (2/6).

We observed failure after the first surgical intervention in 1 patient (3.3%), but this patient was successfully treated later in a second operation. Thus all of the cases were successfully treated. Hospitalization periods of patients with unilateral and bilateral intervention were 2.9 ± 1.2 and 3.3 ± 1.1 days ($p = 0.35$), respectively.

Decreases in serum calcium levels were observed at 24–48 h after operation. All of the patients received calcium treatment. Calcium and vitamin D treatment were given for longer periods to 8 patients as hungry-bone syndrome developed. None of the patients experienced either persistent hypocalcemia or transient or persistent recurrent nerve damage.

Table 2. Free T_3 , free T_4 and sensitive TSH values of the patients

	Patients' values	Normal values
Free T_4 , ng/dl	2.44 ± 0.53	1.45–3.48
Free T_3 , pg/ml	1.10 ± 0.28	0.17–1.85
Sensitive TSH, $\mu\text{IU/ml}$	1.49 ± 1.17	0.49–4.67

Accompanying Thyroid Disease

Nine of the patients who had bilateral intervention had thyroid pathology. Of these 1 patient had Graves' disease, another had toxic multinodular goiter and the remaining 7 patients euthyroid nodular disease. All patients were euthyroid before surgery (table 2). Nearly total thyroidectomy was done on these patients. Unilateral nodular thyroid disease was present in 4 of the unilateral intervention patients. Total lobectomy was done on the lobe with the parathyroid pathology.

Pathological Results

Of the 30 patients, 28 were diagnosed with parathyroid adenoma while hyperplasia was found in only 2. Thyroid malignancy was not found in any of the 30 patients.

Discussion

PHPT defined as a disease characterized by nephrolithiasis in over 50% of cases and osteitis fibrosa cystica in 25% of cases was not common in the past [16]. With the determination of blood hypercalcemia PHPT is readily detectable and may be asymptomatic and therefore may be more common than previously thought. More recently many patients are diagnosed with PHPT but without major findings of renal and skeletal system involvement, osteitis fibrosa cystica and nephrolithiasis ratio of 15–20% [17, 18]. In our series the patients were symptomatic as shown in table 1 and in our previous study in which *Helicobacter pylori* infection was significantly higher in PHPT patients (94.4%) than in our dyspeptic control group [19].

The definitive treatment of symptomatic PHPT is surgery. After extraction of the adenomatous or hyperplastic parathyroid tissues, PTH level returns to normal. Bilateral neck exploration investigating the four glands and extraction of hyperfunctioning glands are accepted as the gold standard for surgical therapy with high success rate [20]. Generally, preoperative localization is not required

for bilateral neck operation [21]. In our study, the total surgical success rate was 96.6%, thereby confirming the previous reports [22, 23].

Our findings of 93% parathyroid pathology leading to PHPT are similar to 80–90% single adenoma reported previously [11, 12]. Extracting adenoma in these cases is usually sufficient for therapy. For this reason some investigators support the idea that unilateral neck exploration is sufficient for PHPT [20, 24]. This procedure can be successful by using preoperative localization methods and/or perioperative gamma hand probe [22, 23, 25]. In addition, intraoperative PTH measurement has been suggested to be useful in excluding multiglandular disease [13]. Unilateral neck exploration can also be done video-assisted or completely by endoscopic interventions. Although bilateral neck exploration has a high cure rate and low morbidity in experienced centers, the trend is towards minimizing intervention. The purpose of minimal invasive intervention is making the incision smaller, decreasing the exploration area, decreasing hospitalization duration and costs [26].

Hyperfunctioning adenoma should be localized for unilateral intervention. Various methods have been used, but none has 100% diagnostic value [6]. The sensitivity of thallium-technetium is between 36 and 76% [27, 28]. ^{99m}Tc-sestamibi scintigraphy was reported to show parathyroidal pathology with 90–95% sensitivity [29]. In our study this sensitivity was found to be 81% while this ratio was 42% for US.

The most important problem between unilateral and bilateral interventions is the possibility of overlooking multiglandular disease in unilateral intervention. Indeed, in one meta-analysis, while multiglandular disease ratio was 20% in bilateral intervention, this ratio was 5% in unilateral intervention [30]. Although it was reported that the measurement of intraoperative PTH level is not a very reliable test as it is emphasized that a premature decrease in PTH can be observed when only one abnormal gland is extracted [30], in a recent review the intraoperative PTH assay was found to be a useful adjunct to preoperative imaging and parathyroid surgery because of its unique ability to detect an occult hyperfunctioning parathyroid tissue [31]. It was also stated that the use of this assay would obviate the need for frozen section histopathology review in most routine cases. The test facilitates minimally invasive parathyroidectomy for single parathyroid adenomas, which, in turn, improves cost-effectiveness and cosmetic outcome. Its use in patients with known preoperative multiglandular disease is promising but requires further study [31]. In a recent study, it was

reported that intraoperative PTH measurement allowed differentiation of single- from multiple-gland disease [32]. We could not measure the PTH levels intraoperatively because of lack of capacity in our laboratory.

It was reported that there were 67 patients with PHPT and concomitant thyroid disease out of 137 patients (49%) in an endemic goiter region. This study emphasized that the localization methods were less sensitive in the patients having thyroid disease. However, combination of sestamibi and US seems most promising in patients with PHPT for localizing an enlarged parathyroid gland and without missing concomitant thyroid disease; this would make it possible to perform minimally invasive parathyroidectomy in the majority of patients suffering from PHPT in an endemic goiter region [33]. In our study, thyroid pathology was also present in a total of 13 patients (43.3%) and we performed thyroidectomy according to thyroid disease type and localization. There was not any positive aspiration biopsy preoperatively and we did not meet any thyroid malignancy in patients postoperatively. We think that thyroid pathologies may have an effect on parathyroidal operation techniques especially in endemic goiter regions.

Conclusion

Our findings indicate that bilateral intervention remains a successful management option without prior localization in patients with PHPT especially in an endemic goiter region.

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