Minimally Invasive Surgery for Treatment of Hyperparathyroidism

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Abstract

Background: Minimal invasive surgery for parathyroidectomy has been introduced in the treatment of hyperparathyroidism.

Objective: To evaluate the contribution of the sestamibi-SPECT (MIBI) localization, cervical ultrasonography, and intraoperative rapid turbo intact parathormone assay in minimal invasive parathyroidectomy.

Methods: Between August 1999 and March 2004, 146 consecutive hyperthyroid patients were treated using the MIBI and ultrasound for preoperative localization and iPTH measurements for intraoperative assessment.

Results: Parathyroid adenoma was detected in 106 patients, primary hyperplasia in 16, secondary hyperplasia in 16, tertiary hyperplasia in 5, and parathyroid carcinoma in 1 patient. Minimal invasive exploration of the neck was performed in 84 of the 106 patients (79.2%) with an adenoma, and in 17 of them this procedure was performed under local cervical block anesthesia in awake patients. Adenoma was correctly diagnosed by MIBI scan in 74% of the patients, and by ultrasound in 61%. The addition of ultrasonography to MIBI increased the accuracy of adenoma detection to 83%. In 2 of the 146 patients (1.4%) iPTH could not be significantly reduced during the initial surgical procedure. Minimal invasive surgery with minimal morbidity, and avoiding bilateral neck exploration, was achieved in 79.2% of patients with a primary solitary adenoma.

Conclusions: Preoperative localizationof the parathyroid gland by MIBI and ultrasound together with intraoperative iPTH measurements resulted in an overall cure rate of 98.6% for the entire series. The addition of ultrasound to the MIBI scan increased the accuracy of adenoma detection.

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The principles of parathyroid surgery were first defined by Felix Mandel in 1926 [1]. He proposed localizing at least four parathyroid glands during surgery and removing only the enlarged parathyroid glands, without biopsy of glands with normal appearance, to avoid permanent hypocalcemia. The gold standard surgical treatment of hyperparathyroidism has since been modified and has evolved to include bilateral cervical exploration, usually under general anesthesia. However, since most cases of primary hyperparathyroidism are caused by a single enlarged primary parathyroid adenoma, several investigators have questioned the need for routine bilateral cervical exploration and recommend the use of unilateral minimal invasive parathyroid exploration [2–4].

Important prerequisites for MIP are preoperative localization of a single parathyroid gland, responsible for sporadic primary hyperparathyroidism in 85%–95% of the patients, and intraoperative measurement of PTH by a rapid PTH assay (iPTH) [5,6]. The increasing sensitivity and specificity of Technetium-99m sestamibi scans (MIBI) with single photon emission computed tomography has yielded accurate preoperative three-dimensional localization of enlarged parathyroid glands [6,7] and allows the surgeon to plan a localized minimally invasive surgical procedure. High-resolution Doppler ultrasonography has also been applied in combination with MIBI, yielding good results in localizing enlarged parathyroid glands in hyperparathyroidism. Ultrasonography performed by an experienced examiner with the purpose of parathyroid localization yielded an accuracy rate of 80–90% [8,9].

With the recent introduction of the rapid parathyroid hormone assay (iPTH), it is now possible to measure PTH levels in the operating room, before and after tumor resection, and to obtain objective evidence of the adequacy of resection [3,4,6]. Thus, minimally invasive parathyroidectomy techniques have become applicable and appear likely to replace conventional bilateral cervical exploration for most patients with hyperparathyroidism.

The present study evaluated the accuracy of the two preoperative localization methods – MIBI in combination with SPECT and ultrasound, and intraoperative iPTH determination – for the purpose of establishing their applicability in focused minimal invasive strategies for treatment of hyperparathyroidism.

Patients and Methods

Patients

Our study group comprised 146 consecutive patients with biochemically verified hyperparathyroidism at the Rambam Medical Center between April 1999 and April 2004. The diagnosis of hyperparathyroidism was established in patients with hypercalcemia and inappropriately high plasma intact PTH levels for serum calcium level. Patients with primary hyperparathyroidism referred for surgery included those with symptomatic disease or those who met the criteria for surgery in asymptomatic primary hyperparathyroidism according to the 2002 National Institutes of Health Workshop on Asymptomatic Primary Hyperparathyroidism [10,11].

iPTH = intact parathormone

MIP = minimal invasive parathyroidectomy
PTH = parathyroid hormone
SPECT = single photon emission computed tomography

Preoperative localization

The vast majority of patients underwent preoperative 99m Tc-sestamibi scans using SPECT (MIBI) and high-resolution Doppler ultrasound. These outpatient procedures provide a three-dimensional reconstruction of the patient and most commonly demonstrate a single adenoma. Relevant anatomic information was noted, including number of glands, size, location, and relationship to adjacent organs.

PTH monitoring

The iPTH levels were monitored before and immediately after induction of anesthesia with a rapid Turbo Intact PTH assay (Diagnostic Products, Los Angeles, USA). Venous samples were obtained from a peripheral site in all patients. The iPTH measurements were repeated 10 minutes after resection of the pathologic gland. A drop in iPTH to normal levels or to less than 50% of the preoperative level, together with frozen section histologic confirmation, were considered proof that the cause for hyperparathyroidism had been eliminated.

Surgical technique

During the initial phase of the study, conventional bilateral cervical exploration was routinely performed under general anesthesia, and in all instances we attempted to identify all four parathyroid glands and resected any enlarged glands. Beginning in March 2001, unilateral exploration using minimal invasive surgery has been used with ever-increasing frequency. This procedure consists of preoperative MIBI and ultrasonographic localization. When both localization procedures were consistent, and after obtaining the patient's consent for regional anesthesia, limited exploration of the neck was undertaken through a 3–4 cm abbreviated unilateral Kocher incision under regional cervical block anesthesia. In patients with a non-localizing MIBI scan or ultrasound, the same minimal invasive procedure was performed under general anesthesia. When both procedures were non-localizing, a conventional Kocher incision was undertaken with bilateral neck exploration under general anesthesia. The goal of this protocol is to identify the single abnormal parathyroid gland using unilateral minimal invasive surgery under local anesthesia, and to remove it. No attempt was made to conduct a conventional bilateral exploration once an enlarged gland had been identified. Once the parathyroid gland that was presumed to be abnormal was removed, a peripheral blood sample for iPTH was obtained 10 minutes after resection. When a post-resection level of iPTH less than 50% of baseline was achieved, the procedure was terminated. If there was an inadequate response, additional iPTH samples were obtained, and if the inadequate response persisted, the exploration was continued on the ipsilateral or contralateral side of the neck and the regional anesthesia converted to general anesthesia. In patients with proven primary or secondary hyperplasia a conventional bilateral neck exploration was performed. In patients who had undergone previous neck exploration through a standard lower cervical incision, a 3 cm lateral vertical incision, anterior to the sternomastoid muscle, was used for resection of the pathologic gland. Frozen sections of the resected specimen were routinely obtained.

Patients undergoing MIP were usually discharged from the hospital on the following day when postoperative hypocalcemia was excluded by clinical and laboratory results. When postoperative hypocalcemia was detected, oral or intravenous calcium and vitamin D were started and the patient was discharged from the hospital only after serum calcium returned to normal levels.

Study protocol

In the present study, data were collected in a prospective database that included symptoms, signs, demographic information, serum calcium, phosphor, PTH, imaging data, anesthetic method, surgical technique, operative and pathologic findings, surgical time, conversion from regional to general anesthesia, postoperative complications, length of hospital stay, and immediate and long-term follow-up data. Patients were released from hospital only after postoperative hypocalcemia was excluded, particularly in patients with secondary hyperparathyroidism. All patients were seen one week postoperatively and in long-term follow-up, at which time serum calcium, phosphor and PTH levels were measured.

Statistical analysis

Differences in operating time and length of hospitalization were computed using the one-way analysis of variance (ANOVA). The Tukey test was used to compare specific differences between subgroups of independent variables. For comparison of the ultrasound and MIBI scores the chi-square test was used. This test was also used for comparison of postoperative calcium requirements. A paired *t*-test was used for comparison of iPTH and calcium levels. A value of $P < 0.05$ was considered significant.

Results

In total, 146 consecutive patients were shown to have hyperparathyroidism, as evidenced by an elevated or inappropriate iPTH level in association with hypercalcemia. The mean age of the 112 (76.7%) women and 34 (23.3%) men was 55.6 $\pm$ 13.7 years (range 20–82 years) in the entire series.

Irrespective of the results of the preoperative localization studies, hyperparathyroidism was cured in 144 of the 146 patients (98.6%). No hyper-functioning parathyroid tissue could be found at surgery (negative surgical exploration) in three patients, in one of whom postoperative PTH dropped to normal while two (1.4%) await further localization studies. In one patient with extreme obesity (140 kg body weight), both imaging studies were negative and after a prolonged cervical exploration only three normal glands were identified. In the second patient with hyperparathyroidism, the MIBI scan was suspicious for a right lower adenoma, but the three glands (including the right lower gland) that were identified after a prolonged surgical exploration showed only minimal hyperplasia, and the postoperative PTH did not drop satisfactorily. This patient awaits further imaging studies before a second neck exploration. In the third patient with hyperparathyroidism, the MIBI and ultrasound imaging studies were negative. At operation only two upper normal parathyroid glands were identified after an extensive prolonged exploration. Although only two glands were identified during surgery, the PTH dropped to normal postoperatively.

On the basis of the post-surgical diagnosis the patients were divided into four groups:

- Group 1: adenoma (106 patients) and carcinoma (1 patient)
- Group 2: primary hyperplasia (16 patients) and multiple endocrine neoplasia type 1 (1 patient)
- Group 3: secondary hyperplasia (16 patients), and tertiary hyperplasia (5 patients)
- Group 4: unidentified diagnosis (1 patient).

MIP was performed in 84 (79.2%) of the patients with parathyroid adenoma, in 17 (16.0%) of whom this procedure was conducted under a regional cervical block. In eight patients a previous unsuccessful cervical exploration had been performed prior to the present neck exploration. In this group of patients the MIP approach was used through a lateral longitudinal incision, anterior to the sternomastoid muscle, according to the preoperative imaging workup, in order to avoid the previous lower cervical exploration scar tissue. Neither MIBI nor ultrasound could predict the exact number or localization of enlarged parathyroid glands in multiple-gland disease due to primary or secondary hyperplasia.

MIBI scans were obtained in 138 (94.5%) patients who underwent standard or MIP explorations. As shown in Table 1 the MIBI scan was diagnostic in 74% of patients in group 1, but in only 18.8% in group 2 ($P < 0.01$) and 38.1% in group 3 ($P < 0.05$). Ultrasound was performed in 116 patients (79%) and was diagnostic in 60.7% in group 1 [Table 1], and in only 6.3% in group 2 ($P < 0.01$) and 19% in group 3 ($P < 0.01$).

Preoperative MIBI localization correctly identified an adenoma in 74.8% of the patients in group 1. The addition of ultrasound to MIBI increased the accuracy of adenoma detection to 83% ($P < 0.05$). In groups 2 and 3 both imaging studies were non-diagnostic in the majority of patients [Table 2].

The iPTH dropped during surgery from 211.7 $\pm$ 172.0 to 37.8 $\pm$ 30.4 pg/ml ($P < 0.001$) in patients with an adenoma, from 179.7 $\pm$ 85.6 to 39.6 $\pm$ 44.4 pg/ml ($P < 0.001$) in patients with primary hyperplasia, and from 1,268.8 $\pm$ 721.8 to 198.6 $\pm$ 173.1 pg/ml ($P < 0.001$) in patients with secondary or tertiary hyperplasia. In two patients (1.4%) the iPTH was not significantly reduced during surgery.

MIP was used in 84 of the 107 patients in group 1 (78.5%), in 17 (9.3%) of whom this procedure was performed under local cervical block. The mean operating time was 76 minutes in group 1, 130 minutes in group 2 ($P < 0.01$) and 108 minutes in group 3 ($P < 0.05$) [Table 3].

Postoperative mean serum calcium levels dropped significantly on the first day following surgery in all groups [Table 4]. Postoperative oral calcium treatment was required in only 18.7% and 25% of patients in groups 1 and 2 respectively, while oral calcium was required in 85.7% of patients in group 3 ($P < 0.01$). Postoperative intravenous calcium treatment was administered to only 10.3% and 6% in patients in group 1 and 2 respectively, while intravenous calcium treatment was necessary in 81% of patients in group 3 ($P < 0.01$). Consequently, the duration of hospitalization in group 3 [Table 3] was also significantly longer than in groups 1 ($P < 0.05$) and 2 ($P < 0.05$).

Table 1. Results of preoperative scans

	Group 1	Group 2	Group 3
Sestamibi (MIBI)			
Diagnostic	74.8%	18.8%	38.1%
Non-diagnostic	19.6%	75.0%	57.1%
Not obtained	5.6%	6.3%	4.8%
High-resolution Doppler ultrasound			
Diagnostic	60.7%	6.3%	19.0%
Non-diagnostic	24.3%	87.5%	23.8%
Not obtained	15.0%	6.3%	57.1%

Table 2. Comparison of sestamibi (MIBI) and ultrasound results

	Group 1	Group 2	Group 3
Both diagnostic	47.7%	0%	14.3%
Only ultrasound diagnostic	9.3%	6.3%	4.8%
Only MIBI diagnostic	14.0%	12.5%	0%
Both non-diagnostic		68.8%	

Table 3. Operative time and duration of hospitalization

	All groups	Group 1	Group 2	Group 3
Operating time (min)				
Minimal	20	20	61	45
Maximal	330	300	330	210
Mean	87	76	130	108
Medium	80	70	110	90
Hospitalization (days)				
Minimal	>1	>1	1	1
Maximal	18	10	6	18
Mean	2.8	2.2	2.4	6.7
Medium	2	2	2	7

Table 4. Pre- and postoperative serum calcium levels

	Group 1	Group 2	Group 3
Preoperative calcium (mg/dl)			
Minimal	10.2	9.7	8.5
Maximal	14.6	12.9	11.8
Mean	11.4	11.4	10.1
Medium	11.3	11.2	10.2
Postoperative calcium (mg/dl)			
Minimal	6.8	7.5	5.3
Maximal	12.8	10.3	10.4
Mean	8.8	8.7	7.1
Medium	8.8	8.6	6.9

Discussion

The purpose of surgical treatment in hyperparathyroidism is to remove enough abnormal thyroid tissue to reduce long-term destructive effects on bone and systemic effects of high calcium, and to keep the patient normocalcemic.

From 1930 to 1990, bilateral cervical exploration of four glands was considered the gold standard management of hyperparathyroidism. A 95–97% rate of success was reported with this approach [12,13], but the operating time was excessive and the hypocalcemia rates remained near 15%. In recent years, the trend toward less

invasive surgery in the management of hyperparathyroidism has become popular among physicians.

The treatment of choice for primary hyperparathyroidism remains a carefully performed exploration by an experienced parathyroid surgeon. The increased sensitivity of parathyroid imaging, together with intraoperative measurement of iPTH, allows the surgeon to plan a localized exploration designed to remove the common single focus of disease by a minimal invasive surgical procedure under local or general anesthesia. The preoperative identification of single-gland disease by a MIBI scan and ultrasound is a prerequisite for any type of limited exploration under local anesthesia. The advantages of this operative approach include unilateral neck dissection, excision of hypersecreting glands only, small incisions, short operating times, local or light general anesthesia, and – even – ambulatory surgery. However, to justify a change from bilateral neck exploration to MIP, the operative success rate of a limited approach must be at least as good as that reported with the traditional procedure. A comparison of the two surgical procedures demonstrated a significant improvement in the surgical success, with a recurrence rate of 3% after 4.2 years [14].

Patients with primary or secondary multi-gland hyperplasia are not offered this technique, and they undergo a classical bilateral neck exploration under general anesthesia. However, if such a patient is encountered during performance of MIP, bilateral exploration can be accomplished with this technique or the procedure can be converted to bilateral exploration under general anesthesia. Adequacy of resection is confirmed by iPTH measurement, and if the biochemical data suggest additional disease the exploration is extended until iPTH levels are reduced to less than 50% of the preoperative level within 10 minutes after gland resection. This is an important adjunct in the operating room because in most patients the MIBI scans and ultrasound imaging modalities miss a second adenoma or multi-gland hyperplasia [7].

In the present investigation, 107 of the patients (87%) with primary hyperparathyroidism suffered from single-gland disease and 16 (13%) from multi-gland disease. Neither MIBI nor ultrasound could predict the exact number and site of involved glands in patients with multi-gland disease, confirming that current localization studies cannot differentiate single- from multi-gland disease [9,15,16]. The MIBI scan identified single-gland disease in 74.8% of patients in group 1, while only 18.8% and 38.1% were diagnostic in groups 2 and 3 respectively. Ultrasonography was diagnostic in 60.7% of the patients in group 1 and diagnostic only in 6.3% and 19% in groups 2 and 3 respectively. The combination of preoperative ultrasound and MIBI increased the predictive positive identification of single-gland disease to 84.1% of patients in group 1, and to 25.1% and 42.9% of patients in groups 2 and 3 respectively. In studies comparing MIBI and ultrasound, the sensitivity of MIBI was 78–83% and that of ultrasound 48–93% [17,18]. Concomitant thyroid disease reduced the results of MIBI from 81% to 75% and the results of ultrasound from 73% to 55% [9,18].

Most patients with secondary hyperparathyroidism and chronic renal failure are controlled non-operatively by calcium and vitamin D intake, restricted phosphate, and treatment with phosphate-binding agents. Surgery is indicated when these measures fail and the patient has intractable bone pain, pruritus, ischemic skin lesions and joint pain. Tertiary hyperparathyroidism occurs in patients with chronic renal failure who have undergone a successful kidney transplant. Tertiary hyperparathyroidism occurs in 1.6–3% of the renal transplant population [20] and can cause significant problems, including pathologic fractures, joint disease, renal calculi, mental status changes, muscle weakness, peptic ulcer disease and pancreatitis. The standard surgical approach for patients with secondary or tertiary hyperparathyroidism has been either subtotal parathyroidectomy or total parathyroidectomy with heterotopic autotransplantation. This strategy is based on the belief that tertiary hyperparathyroidism is generally the result of hyperplasia of all four (or more) glands. However, several studies indicate that in up to 29% of patients with tertiary hyperparathyroidism the disease may be limited to one or two glands [21,22]. Although some surgeons recommend subtotal or total parathyroidectomy with autotransplantation – for fear of recurrent disease in these patients, others propose resection of only the enlarged glands after formal neck exploration [20,23].

In the present study, our strategy for the five patients with tertiary hyperparathyroidism was a formal neck exploration in those with hypercalcemia of more than one year after renal transplantation. At surgery, the size of all glands is evaluated to determine whether the disease is due to single or double adenoma, or hyperplasia. If disease involves only one or two glands, only the enlarged glands are resected and intraoperative iPTH determined to ensure resection of all pathologic glands. In patients with four-gland hyperplasia, a 3.5 gland thyroidectomy was performed and the half-gland was cooled and preserved in liquid nitrogen for future autotransplantation in the event of severe post-surgical hypoparathyroidism. If none of the four glands was identified, then a cervical thymectomy was performed after complete exploration of the neck. With this strategy we were able to locate three ectopic intrathymic glands, and their resection resulted in a significant reduction of iPTH to less than 50% of the initial value within 15 minutes after resection.

Postoperative hypocalcemia is particularly severe in patients with secondary or tertiary hyperparathyroidism. In this group of patients postoperative serum calcium should be especially carefully monitored several times in the early postoperative period and oral or intravenous calcium and vitamin D added as necessary. In 17 of the 21 patients (81%) in group 3, intravenous calcium infusion (8 g per 8 hours) was necessary in the immediate postoperative period to prevent hypocalcemia, while intravenous calcium therapy was needed in only 11 patients (10.3%) in group 1.

Conclusion

Three major technical advances have changed the operative management of hyperparathyroidism: the ability to measure rapid iPTH intraoperatively guides the surgical procedure by predicting outcome, and the combination of preoperative ultrasonography and Tc-99m-sestamibi nuclear scan enables accurate preoperative localization of parathyroid adenomas (83% in our series). The combination of these three techniques enabled the use of minimal

invasive surgery, avoiding bilateral neck exploration in 79.2% of patients with an adenoma, and resulted in a 98% cure rate and minimal morbidity for the whole series.

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