Hypothesis: Directed parathyroidectomy (DP) can be successfully completed in most patients with primary hyperparathyroidism.

Design and Setting: Retrospective review at a tertiary referral center.

Patients: One hundred consecutive patients with untreated, sporadic primary hyperparathyroidism operated on by a single surgeon from April 1, 1999, through December 31, 2001.

Interventions: Following preoperative imaging with sestamibi scintigraphy and ultrasonography, patients underwent parathyroidectomy with intraoperative parathyroid hormone monitoring using a focused approach through a limited neck incision (DP) or bilateral neck exploration (BNE) through a standard collar incision.

Main Outcome Measures: Extent of exploration, operative time, length of stay, morbidity, and cure.

Results: Directed parathyroidectomy was completed in 70 patients and BNE in 30. Bilateral neck exploration was performed as the initial procedure in 13 patients and following intraoperative conversion from attempted DP in 17. Indications for predetermined BNE were failed preoperative localization (n=8) and concomitant thyroid disease that required operative treatment (n=5). The need for predetermined BNE decreased as preoperative localization improved. Intraoperative factors that necessitated conversion to BNE included persistently elevated intraoperative parathyroid hormone levels that accurately predicted multiglandular disease (n=6), incorrect localization (n=5), and inadequate exposure (n=6). Operative time and length of stay were less for DP compared with BNE patients (66 vs 165 minutes and 0.5 vs 1.6 days, respectively). One patient had a temporary vocal cord paresis. All patients were eucalcemic in follow-up (4 months to 3 years).

Conclusions: With accurate preoperative localization and intraoperative parathyroid hormone monitoring, DP can be successfully completed in most patients with sporadic primary hyperparathyroidism. Patients benefit from DP, which reduces operative time and length of stay and facilitates rapid convalescence.

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Challenges in the operative treatment of primary hyperparathyroidism (PHPT) relate to recognition of multiglandular disease (MGD) and location of ectopic glands. For decades surgeons have successfully met these challenges with routine bilateral neck exploration (BNE). The availability of sensitive preoperative imaging techniques and an accurate intraoperative parathyroid hormone (IOPTH) assay challenges this paradigm. These advances facilitate a less extensive operation in patients with uniglandular disease (UGD). To date, directed parathyroidectomy (DP) yields results comparable to BNE. In addition, DP may prove beneficial by reducing operative time, length of hospitalization, and convalescent period. The purpose of this study was to evaluate the efficacy of an algorithm that includes routine preoperative imaging and IOPTH monitoring and is designed to attempt DP in all patients with PHPT.

Methods

During the 3-year period April 1, 1999, through December 31, 2001, a single surgeon (W.H.S.) treated 100 consecutive patients with sporadic PHPT. A standardized perioperative management algorithm was applied to each patient (Figure 1). Patients with persistent or recurrent PHPT and those with mediastinal parathyroid glands identified on preoperative imaging were excluded. Each patient underwent preoperative imaging with sestamibi scintigraphy and ultrasonography. Both studies were obtained...
with the patient supine and neck extended. The same 2 radiologists (L.W. and D.M.) interpreted all imaging studies.

The scintigraphy technique included dynamic planar imaging of the neck and chest during intravenous isotope injection (20 mCi [740 MBq] of technetium Tc 99m sestamibi). These images were acquired at 3-second intervals for 2 minutes in a 128 × 128 matrix. A 10-minute planar image of the neck was then obtained in a 256 × 256 matrix. Planar images with a sternal notch marker in place were repeated 2 hours after injection. Early in the study period, single-photon emission computed tomography (SPECT) imaging was also performed 2 hours after injection. This aspect of the technique was later modified to 30 minutes after injection. The SPECT images were obtained with 6° angular rotation using parallel hole collimators on a dual head camera. Ultrasound examinations were performed using a 7.5- or 12.5-MHz linear array transducer, with images obtained in longitudinal and transverse planes.

Patients in whom the preoperative imaging studies (one or both) suggested UGD underwent parathyroidectomy using a focused approach through a limited neck incision (DP). Patients in whom the preoperative imaging studies were negative or equivocal underwent parathyroidectomy with BNE through a standard collar incision (predetermined BNE). Patients with a thyroid nodule detected by palpation and/or ultrasonography (size >1 cm or nodule with fine calcifications) underwent fine-needle aspiration. Patients with a symptomatic goiter or positive fine-needle aspiration results (malignant or indeterminate) underwent predetermined BNE and concurrent thyroidectomy.

Intraoperative parathyroid hormone monitoring was performed in all cases with the Immulite Turbo intact PTH assay (Diagnostic Products Corp, Los Angeles, Calif) using a multipurpose analyzer (Immulite 1000). Blood samples were obtained from a lower extremity intravenous catheter for IOPTH measurements before incision (baseline) and 5 and 10 minutes following gland excision. During the study period, the practice of obtaining a second baseline (following dissection of the abnormal gland) was abandoned when a reliable increase in IOPTH from the first baseline could not be demonstrated. Directed parathyroidectomy was completed when the IOPTH percentage decrease from baseline exceeded 30% and the final IOPTH value reached the reference range. If these criteria were not met 10 minutes following gland excision, a 20-minute sample was obtained. If these criteria were still not met, DP was converted to BNE.

Only patients following completed DP were candidates for same-day discharge. Follow-up included outpatient visits 2 and 8 weeks postoperatively, at which time calcium and PTH levels were measured. Subsequent follow-up information was obtained from the referring physician. The following variables were retrospectively reviewed: (1) factors that determine the extent of exploration, (2) operative time, (3) length of stay (LOS), (4) morbidity, and (5) biochemical cure. Mean and range of values were calculated for numerical data. Statistical comparisons between patient groups were performed using a 2-tailed t test.

RESULTS

PREOPERATIVE

The study group consisted of 76 women and 24 men with a mean age of 58 years (range, 14-83 years). Clinical manifestations of PHPT included neuropsychiatric symptoms (74%), decreased bone density (57%), nephrolithiasis (24%), and others (29%). The mean preoperative calcium and parathyroid hormone (PTH) levels were 11.2 mg/dL (2.80 mmol/L) (reference range, 8.4-10.2 mg/dL [2.10-2.55 mmol/L]) and 163.3 pg/mL (17.20 pmol/L) (reference range, 12-72 pg/mL [1.26-7.58 pmol/L]), respectively.

In the 86 patients with a single focus of abnormal sestamibi uptake, scintigraphy correlated with the intraoperative findings in 74 (86%). Of the 9 patients with multiple foci of abnormal uptake, 5 had UGD detected during DP guided by the most convincing imaging abnormality. In the remaining 4 patients, 2 had MGD detected during predetermined BNE for equivocal imaging and 2 following conversion to BNE for persistently elevated IOPTH levels. The 5 patients with negative sestamibi scans underwent predetermined BNE, at which time UGD was found in 4 and MGD in 1.

In the 76 patients with a single sonographic parathyroid abnormality, ultrasonography correlated with the intraoperative findings in 67 patients (88%). Of the 9 patients with multiple abnormalities, 4 had UGD detected during DP guided by the most convincing imaging abnormality, 2 following conversion to BNE for incorrect localization, and 1 during predetermined BNE for equivocal imaging. The remaining 2 patients had MGD detected following conversion to BNE for persistently elevated IOPTH levels. Of the 15 patients with negative ultrasonic examinations, 6 had UGD detected during DP guided by sestamibi scan alone, 5 during predetermined BNE for negative imaging, and 2 following conversion to BNE for incorrect localization by sestamibi scintigraphy. The remaining 2 patients had MGD detected during predetermined BNE for negative imaging.

The 2 imaging modalities were concordant in 81 patients, for the same single abnormality in 76 and for more than one focus in the remaining 5. Directed parathyroidectomy in these 5 patients was based on the most convincing abnormality. At DP, concordant studies correlated with the intraoperative findings in 71 patients (88%). In the remaining 10 patients, conversion to BNE was required in 6 for MGD identified with IOPTH monitoring and in 4 for incorrectly localized UGD.

In the first 50 patients (April 1, 1999–December 31, 2000), sestamibi scintigraphy and ultrasonography correlated with the intraoperative findings in 70% (n=35) and 60% (n=30), respectively. In the latter 50 patients (January 1–December 31, 2001), sestamibi scintigraphy and ultrasonography correlated with the intraoperative findings in 78% (n=39) and 75% (n=38), respectively.
Directed parathyroidectomy was attempted in 87 patients based on findings on both imaging studies (n=81), sestamibi scintigraphy alone (n=5), or ultrasonography alone (n=1). Directed parathyroidectomy was completed in 70 patients and converted intraoperatively to BNE in the remaining 17. The percentage of DP procedures increased over time (Figure 2A). Of the 70 DP procedures, 61 were performed through a limited suprasternal incision. The remaining 9 procedures were performed through an upper lateral incision with the aid of preincision sonographic marking of the skin overlying the enlarged parathyroid gland.

Bilateral neck exploration was performed in 30 patients, as the initial procedure in 13 and following intraoperative conversion of an attempted DP in 17. Indications for predetermined BNE were failed preoperative localization (n=8) and concomitant thyroid disease that required operative treatment (n=5). Reasons for failed preoperative localization included small parathyroid adenomas (weight, <300 mg) (n=4), MGD (n=2), and concomitant multinodular goiters (n=2). Concomitant thyroid disease included follicular neoplasm (n=3), papillary thyroid cancer (n=1), and multinodular goiter (n=1). Intraoperative factors that necessitated conversion from DP to BNE included persistently elevated IOPTH levels that predicted MGD (n=6), incorrect localization (n=5), and inadequate exposure (n=6). The need for predetermined BNE decreased over time (Figure 2B). Fewer intraoperative conversions to BNE were required in the latter half of the study period (January 1–December 31, 2001) (Figure 2C).

In the 91 patients with UGD, the mean IOPTH level and percentage decrease 10 minutes following gland excision were 38.4 pg/mL (4.04 pmol/L) (range, 1.0-183.0 pg/mL [0.11-19.27 pmol/L]) and 82.0% (range, 50.6%-98.0%), respectively. Eight UGD patients required a 20-minute sample, at which time the mean IOPTH level and percentage decrease were 50.1 pg/mL (5.28 pmol/L) (range, 38.8-60.0 pg/mL [4.09-6.32 pmol/L]) and 83.9% (range, 70.4%-95.4%), respectively. Multiglandular disease was found in all 6 patients who required intraoperative conversion from DP to BNE for persistently elevated IOPTH levels. In these patients, the mean IOPTH level and percentage decrease 10 minutes following excision of the first gland were 131.7 pg/mL (13.87 pmol/L) (range, 81.0-216.0 pg/mL [8.53-22.74 pmol/L]) and 39.1% (range, 23.7%-60.7%), respectively. Multiglandular disease was detected in the remaining 3 patients at the time of predetermined BNE. Results of imaging and IOPTH monitoring in the 9 patients with MGD are summarized in Figure 3.

The mean operative time for the DP procedures was 66 minutes (range, 35-135 minutes) compared with 165 minutes (range, 75-270 minutes) for all BNE procedures (P<.001) and 139 minutes (range, 75-201 minutes) for predetermined BNE procedures alone (P<.001).
The mean operative time for predetermined BNE procedures excluding those with concomitant thyroidectomy was 118 minutes (range, 75-195 minutes).

POSTOPERATIVE

The mean LOS for DP patients was 0.5 days (range, 0.5-2.0 days) compared with 1.6 days (range, 1.0-9.0 days) for BNE patients ($P < .001$). All patients were eucaloric in follow-up (4 months to 3 years). No patient had permanent hypoparathyroidism. The mean postoperative calcium and PTH levels for the study group were 9.4 mg/dL (2.35 mmol/L (range, 8.4-10.2 mg/dL [2.10-40.80 mmol/L]) and 68.1 pg/mL (7.17 pmoL/L) (range, 11.0-203.0 pg/mL [1.16-21.38 pmoL/L]), respectively.

A single patient had a transient vocal cord paresis following DP converted to BNE for incorrect localization. This resolved 4 months postoperatively without treatment. A single patient had a subplatysmal hematoma that required a subsequent operation following BNE, and 3 patients had seromas that required aspiration following BNE (one with concomitant total thyroidectomy). There were no wound complications following DP.

COMMENT

Unilateral exploration was the first operative strategy to take advantage of the high frequency of UGD in patients with PHPT and limit the extent of exploration. With this approach, visualization of a normal gland ipsilateral to the presumed adenoma is believed to exclude MGD and thus eliminate the need to explore the contralateral side. The longstanding criticism of this approach has been the possibility of missing contralateral abnormal glands. To more definitively account for the possibility of MGD and its relationship with the thyroid. Despite improvement in preoperative imaging, certain pitfalls remain. Both imaging modalities may be inaccurate in the setting of small parathyroid adenomas (<300 mg), MGD, and nodular thyroids.

Despite improvement in preoperative imaging, the inability of these imaging modalities to detect MGD argues against image-guided exploration alone and emphasizes the need for an intraoperative adjunct to exclude MGD. In our series, 6 cases of persistent PHPT due to MGD would likely have resulted from image-guided exploration alone without IOPTH monitoring. These data and others support the ability of IOPTH monitoring to identify MGD. This is particularly true when stricter criteria (levels that decrease >50% and reach the reference range) are used. Requiring a decrease into the reference range did not lead to unnecessary BNE in our experience, although others have found this to be the case.

In a previous blinded prospective study from our institution, in which PTH levels were collected during traditional BNE in 72 patients, only 4 patients with MGD would have been missed if IOPTH-directed procedures had been performed. The second enlarged glands in these 4 patients varied between 70 and 210 mg. The IOPTH level decreased inappropriately after the removal of the initial enlarged gland in these patients. It is, of course, not known whether these glands were or would have become hyperfunctioning to subsequently produce persistent PHPT had they been left in situ. There is a trend toward replacing the traditional definition of MGD based...
on morphologic criteria with a functional definition based on IOPTH monitoring. With this concept in mind, IOPTH monitoring may also be useful during conventional exploration to limit the extent of exploration and tissue resection. The currently reported incidence of MGD appears to vary, depending on the surgical approach (focused vs bilateral exploration) and the defining criteria (IOPTH hypersecretion vs size).

In this series, we compared the operative time and LOS for DP vs BNE and found that both were less with DP. Since the BNE patients in this series may be more complex (ie, failed localization), the validity of such a comparison may be affected. Therefore, we reviewed previous data from our institution on a group of patients with PHPT who underwent traditional BNE without preoperative imaging. The mean operative time for those patients was 204 minutes, and no patient was discharged the day of surgery. In comparison, the mean operative time and LOS for the DP patients in the present series were 66 minutes and 0.5 day, respectively. Thus, in our hands, these advantages of DP held true.

In conclusion, accurate preoperative localization and IOPTH monitoring facilitate successful DP in most patients with sporadic PHPT. Although the safety and efficacy of DP are comparable to BNE to date, a precise definition of its durability requires longer follow-up. Only then will the prevalence of MGD be definitively answered. In addition, scarring from the small area of dissection required for DP is not likely to compromise the efficacy and safety of subsequent parathyroid or thyroid operations should they become necessary. Until further data demonstrate inadequacies with this approach, DP is our procedure of choice in patients with sporadic PHPT. When successfully completed, DP reduces operative time and LOS and facilitates rapid convalescence.

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REFERENCES


Quan-Yang Duh, MD, San Francisco, Calif: I want to congratulate Dr Burkey and her colleagues for a timely study that is well analyzed and presented. First of all, their operative success rate of 100% is very impressive, with all patients eucalcemic postoperatively and no permanent complications. In addition, this study shows that, using preoperative sestamibi scan or ultrasound and intraoperative PTH monitoring, 70% of patients with primary hyperparathyroidism can undergo a successful parathyroidectomy by a limited exploration, instead of the traditional bilateral neck exploration identifying all 4 glands. The algorithm they propose is similar to what many endocrine surgeons are currently using. In a survey of endocrine surgeons presented by Leigh Delbridge of Sydney, Australia, at the International Association of Endocrine Surgeons meeting in Brussels last year, more than half (56%) of the endocrine surgeons surveyed said they were performing “minimally invasive parathyroidectomy.” More than 90% (92%) were using techniques similar to what Dr Burkey described here, a scan-directed limited neck exploration, without using the videoscope. In addition to limited, others have also called this scan-directed, minimally invasive, directed, concise, or focused parathyroidectomy. Dr Burkey’s results validate this trend of limited exploration, and this excellent paper will be a classic, to be cited to support this modern approach to parathyroidectomy.

I agree that a focused, scan-directed parathyroidectomy takes less time and causes less tissue trauma than bilateral exploration and should be performed whenever possible. However, using the 30 patients who underwent bilateral exploration in this study as a control group exaggerates the advantages of the scan-directed focused parathyroidectomy. These 30 patients underwent bilateral exploration because of various complex issues, including multiglandular parathyroid disease, comitant thyroid diseases, small parathyroid adenomas that could not be localized, or adenomas that were incorrectly localized by preoperative scans. Since these 30 patients are clinically more complex, it should not be a surprise that they need longer operating time and longer hospital stay. A scan-direct parathyroidectomy selects a subgroup of patients who are less complex for the procedure. Using these 30 patients who are more complex as a control group would violate the intent-to-treat principle when comparing procedures.

I have 3 questions for the authors. The first question concerns intraoperative PTH assay. Your intraoperative PTH assay correctly identified all 6 patients with multiglandular parathyroid diseases who were not identified by preoperative scans, thus avoiding a failed operation. Also none of the patients with single adenoma had an inadequate drop of PTH (which would have led to an unnecessary bilateral neck exploration). This 100% sensitivity and 100% specificity are astonishing. This is an area of controversy. Some endocrine surgeons have found IOPTH to miss about half of the multiple adenomas, leading to persistent hyperparathyroidism and causing unnecessary bilateral ex-
ploration in more than 5% of patients with single adenoma. What is the trick to achieve such excellent results for IOPTH?

The second question concerns concordant findings on preoperative sestamibi scan and ultrasonography. Of the 71 patients with concordant scans, there were 10 failures of localization, 6 missed multiglandular diseases, and 4 incorrect localizations. In our experience with concordant scans, we miss multiglandular disease in about 5% of the patients, but we did not have any incorrect localization. Sometimes the radiologists correctly identify whether the adenoma is in the right or left side of the neck but misidentify whether it is an upper or lower gland. In these 4 concordant adenomas that were incorrectly identified, were they in the same side of the neck as predicted by the scans or were they in the opposite side of the neck?

The third question concerns incision length. One of the advantages for a limited exploration is a shorter incision. As alluded to yesterday by Dr van Heerden, in the paper “Mine is Smaller Than Yours” presented by Dr Laurent Brunaud at this year’s meeting of the British Association of Endocrine Surgeons in Pisa, at UCSF [University of California, San Francisco] patients who underwent focused parathyroidectomy had incision length 1.3-cm shorter than those who underwent standard bilateral exploration (average, 2.8 vs 4.1 cm). What size incision do you usually use for the limited parathyroidectomy?

Again, I want to congratulate Dr Burkey and her colleagues for a superb paper showing us that a scan-directed focused parathyroidectomy is safe and effective, and it can be achieved in more than 70% of patients with primary hyperparathyroidism.

Leigh A. Neumayer, MD, Salt Lake City, Utah: You mentioned that you measure IOPTH every 5 minutes, and that is a little different than what most people do. Maybe that is partially an answer to Dr Duh’s question, but in the data that you showed us at least, it looked like the majority of patients had their drop at 10 minutes. So I am wondering, now that you have 100 patients, are you still measuring every 5 minutes and how much does that cost? And how quickly does your lab get the results back?

Melanie Richards, MD, San Antonio, Tex: I commend Dr Burkey on an excellent presentation with superb results. Your ultrasonographers and nuclear medicine staff are able to localize 86% and 88% of abnormal parathyroid glands. Why obtain both of these studies with them being concordant 88% of the time? If they are discordant, are you not going to do a bilateral exploration anyway, depending on the PTH results?

In addition, by performing ultrasonography on all of your patients, are you picking up more thyroid nodules that may be benign and perhaps doing more thyroid resections than may be necessary? What are your recommendations for an FNA [fine-needle aspiration]? Are you obtaining biopsy specimens on all patients who have thyroid nodules or abnormalities found on ultrasound, or do you have a parameter for recommending a biopsy, such as more than 1 cm?

Richard A. Prinz, MD, Chicago, Ill: In your presentation, you said that equivocal imaging would lead you to do a bilateral neck exploration. I really don’t know what you mean by equivocal. Do you have to have both the sestamibi scan and the ultrason sound concordant, or will you rely on one positive study?

My second question deals with the issue of the concomitant thyroid nodule. In the patients I see who have hyperparathyroidism and a palpable thyroid nodule, I think they are best treated by removing that nodule since you are already operating on the neck. They are one subset of patients in whom I don’t do fine-needle aspiration. Can you please comment on the risks of leaving a palpable thyroid nodule?

Dr Snyder: Dr Prinz, members, and guests, we appreciate the opportunity to present these data to you. Dr Duh’s initial question related to multiglandular disease and how we caught them all with IOPTH. The answer is, I think, that we insist that the IOPTH is not only less than half the baseline but in the normal range. The one patient with multiglandular disease who dropped more than 50% from baseline had a PTH of 81, which is above our normal values.

The reason that we haven’t had to unnecessarily extend to a bilateral neck exploration in patients with uniglandular disease is that in those patients who are higher than normal or haven’t dropped at 10 minutes we extend our time to 20 minutes following the baseline level. If the level hasn’t decreased more than 50% from baseline and into normal range by 20 minutes, they have turned out to have multiglandular disease. Most of the patients with uniglandular disease drop by 10 minutes.

Regarding the incorrect locations in the 4 patients with uniglandular disease that Dr Duh asked about, 2 were on the contralateral side and 1 was in the thymus and difficult to find even with a bilateral neck exploration. Its site had been incorrectly localized elsewhere. Localizations are sometimes confused by overlying thyroid nodules or, as most of you know, the radiologists think they see something that represents an abnormal parathyroid gland and in fact it turns out to be a thyroid nodule. With increasing experience, our radiologists are getting better and better at sorting this out.

At the same time I will deal with Dr Prinz’ question and I think Melanie Richards also asked about the management of concurrent thyroid nodules. We fine-needle those that are greater than 1 cm, single nodules, or a dominant nodule that is substantially bigger than the others, or if they contain calcifications in the nodule. We have a very capable radiologist who decides which ones ought to be needle aspirated. We have discussed this many times and agree on the criteria. One of the advantages of this smaller, more limited approach, is that if one has to go back and do a thyroidectomy at a later time, it is not importantly complicated by the small incision and minimal dissection required by the directed approach. We have not been back on anybody yet, but the small limited dissection, I think, will not present a problem if reoperation becomes necessary.

Regarding Dr Duh’s question about incision length, they turn out to be around 3 cm. However, I don’t think the length of the incision, as Dr van Heerden alluded to yesterday, really is very important. What is important is the extent of the dissection. The much more limited dissection that occurs with a directed parathyroidectomy is less morbid, and the patients con valesce more quickly. It isn’t the size of the incision but the extent of dissection.

Dr Neumayer, regarding your question about the frequency of obtaining the PTH levels, Dr Burkey tried to describe it by saying every 5 minutes. We don’t get them every 5 minutes. We get samples 5 minutes and 10 minutes after the abnormal gland is removed. Then, if the PTH hasn’t dropped to the prescribed levels of half of baseline and into the normal range, we get one at 20 minutes. And I think that is what Dr Burkey was meaning to say. If the IOPTH hasn’t dropped to those levels at 20 minutes, then we convert to a bilateral neck exploration. We sort of learned this in the process and particularly those people who start with very high parathyroid hormone levels, they just don’t drop that fast. It seems to take about 20 minutes for the IOPTH to drop from a PTH of 600 or 700 to the normal range.

Dr Prinz, we defined equivocal as those studies that only vaguely suggested one or more sites that were not corroborated by the other study.