

Is intraoperative parathyroid hormone monitoring necessary in symptomatic primary hyperparathyroidism with concordant imaging?

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ABSTRACT

Introduction: Symptomatic primary hyperparathyroidism (PHPT) is still seen frequently in referral centers all over India. These patients require parathyroidectomy and this study aimed to assess the roll of intraoperative parathyroid hormone (PTH) assay when concordant results of two localization studies were available. **Study Design:** We analyzed the case records of patients who underwent parathyroidectomy for PHPT from January 2005 to June 2015. **Results:** Of 143 patients included in the study, technetium 99m methoxyisobutylisonitrate dual phase scintigraphy showed true positive images in 93.7% and high definition ultrasonography in 84.6% of patients. Concordance in localization studies was observed in 121 (84.6%) patients, successful parathyroidectomy was done in 117 (96.7%) patients with concordant localization studies. Intraoperative PTH monitoring showed 97.84% sensitivity and 75% specificity and predicted failure in 2 patients with concordant imaging. However, re-exploration was not successful in these patients. **Conclusion:** When concordant result is available between parathyroid scintigraphy and anatomical imaging surgical cure rate is high in trained hands. Re-exploration is unlikely to be successful since these patients require higher imaging.

Key words: Concordant imaging, hyperparathyroidism, parathyroidectomy, parathyroid hormone assay

INTRODUCTION

Primary hyperparathyroidism (PHPT) is still a symptomatic disease in India.^[1] Diagnosis of PHPT is usually delayed due to relative rarity and varying presentations. A good number of these patients developed major deformities resulting in loss of job and financial constraints. These patients were essentially the candidates for surgical treatment. Regional anesthesia was not an option in most of the patients due to the size of parathyroid lesion, frequent occurrence of adhesion to surrounding tissues, and

coincident thyroid pathologies. The prevalence of renal dysfunction, gastrointestinal illnesses, diabetes mellitus, and hypertension was high among PHPT patients. Most of the patients belonged to the American Society of Anesthesiologists grading II and III and risk of anesthesia was high due to possible electrolyte changes and worsening of renal function.^[2,3]

Preoperative localization studies were routinely done to reduce the operating time and to avoid unnecessary dissection. Our protocol included technetium 99m methoxyisobutylisonitrate dual phase scan (MIBI scan) and ultrasonography before operation. Ultrasonography was performed jointly by surgeon and sonologist. Parathyroidectomy was done under general anesthesia and

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Intraoperative parathyroid hormone monitoring (IOPTH assay) was done to ensure the completeness. The institutional financial audit showed that the localization studies and IOPTH assay accounted for 18.5% of the total cost of treatment.

Aim of the present study was to assess the use of IOPTH assay when concordant imaging was available. We hypothesized that cure rate of PHPT is above 95% when concordant imaging was available and IOPTH assay might not positively influence the outcome.

Study design

We included patients who were successfully operated for primary symptomatic hyperparathyroidism from January 2005 to December 2014. Patients who had phenotypic expressions of multiple endocrine neoplasia Type 1 and 2 were excluded. Patients with evidences of chronic kidney disease were also excluded. Clinical and biochemical data were collected from the database maintained by Endocrine Surgery division.

Preoperative localization

Fifteen to twenty mCi of ^{99m}Tc-MIBI was injected intravenously and high resolution images from anterior neck and mediastinum were acquired using dual head variable gamma camera. Images were collected at 20 min and 2 h after injection.

Ultrasound (US) imaging using 7.5–10 MHz probe was done by surgeon and trained sonologist together. Precise location of lesion and its relationships to neighboring structures were recorded. Thyroid gland was examined for nodules and guided aspiration for cytology was done.

When scintigraphy recorded mediastinal parathyroid lesion, magnetic resonance imaging (MRI) was used as anatomical imaging. Concordance in imaging was recorded when scintigraphy features were identical with anatomical imaging in site and number.

Surgical strategy

Focused parathyroidectomy with IOPTH monitoring was done for a single parathyroid lesion with concordant imaging. Focused parathyroidectomy was attempted in patients with discordant imaging if scintigraphy or anatomical imaging showed a single suspicious lesion. IOPTH monitoring was also done with an intention to convert to total neck exploration (TNE) if indicated.

TNE was done when both imaging were inconclusive with IOPTH monitoring. Cervical exploration was done first when mediastinal lesion was suspected followed by median sternotomy if necessary. IOPTH monitoring was also done.

Intra-operative parathyroid hormone monitoring

The preincision blood sample was drawn from the peripheral vein before induction. The postexcision blood sample was drawn from the peripheral vein 10 min after the excision of the lesion. More than 50% decline of postexcision PTH value was considered positive for completeness of excision. Rapid PTH assay was done by chemiluminescent micro-particle immunoassay (ARCHITECT I System using ABBOTT reagent).

Terminology used to report test result was based on Carter AB and Howanitz PJ recommendation^[4]

- True decline-diagnostic PTH decline in a patient free of hyperfunctioning parathyroid tissue
- False decline-diagnostic PTH declines below cut-off with residual hyperfunctioning parathyroid tissue *in situ*
- True failure to decline-failure to decline past cut-off with functioning residual parathyroid tissue
- False failure to decline-failure of PTH to decline past cut-off in a patient free of hyperfunctioning parathyroid tissue.

Patient is considered cured if serum corrected calcium levels remained <10.2 mg/dl in the postoperative period and also 6 months after operation. Serum PTH estimation was done if serum calcium level was above 10 mg/dl.

Statistical analysis

For the comparison of categorical variables among the different groups, Chi-square test was used. For continuous/numerical variables with two groups, Mann–Whitney U-test was applied, because the laboratory values did not follow the parametric assumption. SPSS version 11 (IBM Corporation) was employed for statistical analysis.

RESULTS

We analyzed data of 143 patients with a median age of 46 years (11–80) and male and female sex ratio of 1:1.46. Of the group, 28 (20%) patients were receiving treatment for hypertension and 15 (11%) for diabetes mellitus before the diagnosis of PHPT was made. Thirty three (23%) patients had palpable neck swelling. All patients had normal renal function and mean estimated glomerular filtration rate was 79.54 ml/min/1.73 m² (standard deviation [SD] 39.54). Laboratory values of the group are noted in Table 1. Seventy two patients (50.7%) had calcium elevated above 12 mg/dl and 88 (62%) had serum PTH elevated above 350 pg/ml.

Localization studies

MIBI scan showed positive imaging in 136 (95%) patients and inconclusive in 7 (5%) patients. The operation findings matched well in position and number with MIBI

findings in 134 (93.7%) patients and this included 3 double adenoma and 13 ectopic lesions. MIBI images correctly predicted superior parathyroid lesions in 21 patients. The high serum PTH level positively influenced MIBI scan while coincident thyroid disease negatively affected it [Table 2]. On correlating with histology, MIBI scan showed inconclusive results 8 adenomas and 1 carcinoma. MRI scan did not identify the second lesion in a patient with mediastinal double adenoma.

US identified lesions in 121 (84.6%) patients and was inconclusive in 22 (14.4%). High serum PTH level positively influenced US localization [Table 3]. US localization matched correctly with operation findings in 121 patients. US detection rate was 91% when the mediastinal lesions were excluded. US detection rate was not significantly influenced by co-existing thyroid diseases and size of parathyroid lesion. MIBI/US concordant images were seen in 113 (83.7%) patients.

MRI was used as anatomical imaging for 8 patients with mediastinal parathyroid lesions located by MIBI. MRI could locate mediastinal lesions in all patients. There was concordance of MIBI with anatomical imaging

Table 1: Biochemical profile of the study group

Feature	Value	SD	Reference level
Serum calcium (mg/dl)	12.346	1.7501	8.6-10.2
PTH (pg/ml)	875.74	777.87	15-68
PO ₄ (mg/dl)	2.529	0.839	2.7-4.5
25-OHD (ng/ml)	26.838	75.516	30-45

SD: Standard deviation, 25-OHD: 25-hydroxy vitamin D, PTH: Parathyroid hormone

Table 2: Features influencing methoxyisobutylisonitrate scan

Features	MIBI positive	MIBI negative	P
Mean serum calcium (mg/dl)	12.354 (1.751)	11.72 (1.345)	0.2892
PTH (pg/ml)	872.45 (234.13)	347.22 (214.989)	0.001
Size (cm)	3.63 (3.290)	2.75 (1.197)	0.427
Weight (g)	5.245 (5.0293)	2.77 (1.198)	0.144
Thyroid lesions (%)	36 (27.1)	6 (66.7)	0.020
Total	134	9	

MIBI: Methoxyisobutylisonitrate, PTH: Parathyroid hormone

Table 3: Features influencing ultrasound

Features	US positive	US negative	P
Serum calcium	12.361 (1.744)	12.29 (1.478)	0.845
PTH	872.16 (778.690)	523.10 (599.405)	0.047
Thyroid disease (%)	32 (26.6)	10 (45.45)	0.067
Size	3.11 (1.198)	3.00 (1.272)	0.572
Weight	5.31 (5.031)	5.80 (6.434)	0.697
Total	121	22	

US: Ultrasound, PTH: Parathyroid hormone

in 121 (84.6%) patients. Both MIBI scan and US were inconclusive in two patients.

Operation

Surgical procedures included focused parathyroidectomy 106 (74%), parathyroidectomy with ipsilateral hemi-thyroidectomy 22 (15.5%), sternotomy and parathyroidectomy 6 (4%), TNE 6 (4%), and parathyroidectomy with total thyroidectomy 5 (3.5%), respectively. Indication for hemi-thyroidectomy was adherent parathyroid lesion in 14 and co-existing thyroid nodule of suspicious cytology in 8. Total thyroidectomy was done for patient with large volume goiters (n: 3) and papillary thyroid cancer (n: 2). Double adenomas were removed in 2 patients. Mean duration of surgical procedure was 44.42 min (SD: 18.561).

Parathyroid lesions were hard and adherent to soft tissues or thyroid in 23 patients. Mean size of the lesion was 2.78 cm (1–8) and weight was 5.069 g (1–27).

The mean preincision serum PTH values was 951.274 pg/ml (SD: 849.255) and 10 min postexcision was 207.8 pg/ml (SD: 367.031).

Results of IOPTH assay showed true decline = 136, false decline-1 true failure to decline-3, and false failure to decline-3, respectively. IOPTH monitoring showed 97.84% sensitivity and 75% specificity in predicting completeness of excision. The positive predictive value was 99.27% and negative predictive value was 50%. The mean of basal serum PTH done initially (875.74; SD 777.87) was not statistically different from preincision values ($P = 0.478$).

On review after 6 months, 139 (97.2%) were normocalcemic and PTH levels were within normal limits. Four patients had persistent hypercalcemia.

Final histology noted adenoma 126 (88.1%), hyperplasia 3 (2%), atypical adenoma 6 (4%) and carcinoma in 10 (6.8%) patients. Histology of one patient showed normal parathyroid gland. This included 3 instances of double adenomas.

Individual case studies of patients with persistent hypercalcemia is noted below.

Case 1: A 64-year-old lady showed concordant MIBI/US imaging for left inferior parathyroid lesion. However, thyroid gland showed coarse heterogeneous echo texture and lobulated contour. The PTH level declined marginally (3 pg/ml). Histology showed 5 mm size normal parathyroid. TNE failed to identify another lesion.

Case 2: A 39-year-old male patient showed concordant MIBI/US images corresponding to both inferior parathyroid glands. TNE was done and removed 2 cm (3.5 g) lesion from right side but failed to locate lesion on left side. There was 25% decline of PTH levels after excision. Other parathyroid glands were normal in size and shape. The right side lesion was reported as adenoma.

Case 3: A 35-year-old lady had mediastinal parathyroid lesion on MIBI and was concordant with MRI. Median sternotomy and excision of 3 cm (3.5 g) lesion close to aortic arch was done. PTH level declined to 60% of preincision values but had persistent hypercalcemia. Histology revealed parathyroid adenoma. Repeat MIBI showed a second mediastinal lesion posterolateral to descending aorta and was removed by re-exploration after 6 months. This lesion was reported as adenoma.

Case 4: A 36-year-old lady had right inferior parathyroid lesion with concordant MIBI/US images. Exploration showed 2.5 cm lesion adherent to thyroid lobe. Right hemi-thyroidectomy and excision of the tumor was done. There was no decline of PTH values postoperatively. Histology showed parathyroid carcinoma invading thyroid lobe and soft tissue. Computed tomography of chest showed multiple scattered lung nodules and lytic lesion of T12 vertebra. Guided aspiration from lung and vertebra showed features suggestive of metastases from parathyroid carcinoma. Patient was on palliative care.

DISCUSSION

Patients with symptomatic PHPT differ from those with asymptomatic variant in general health status and features related to parathyroid pathology. Patients are younger with poor general health indices and have high incidences of Vitamin D deficiency.^[5-7] Parathyroid lesions are larger and heavier compared to those of asymptomatic patients. The spectrum of parathyroid pathologies in PHPT include single-gland adenomas (80–85%), multi-gland hyperplasia (10–15%), and carcinomas (1%).^[8] A systematic review of 20,225 PHPT patients showed single adenoma (88.9%), multi-glandular nodular hyperplasia (5.74%), multi-glandular adenomas (4.14%), and carcinomas (0.74%).^[9] Milas M *et al.* observed 13% incidence of double adenomas with a predilection for superior parathyroid glands.^[9] Many published series from India observed 4% to 6% prevalence of carcinomas and <6% prevalence of multi-glandular lesions^[10-13] among symptomatic PHPT patients. Double adenomas were noted in 4 patients of present series. Sporadic multi-glandular nodular hyperplasia is rare among symptomatic patients.

We observed similar parathyroid pathologies in patients who had phenotype expressions of MEN type 1.

Technetium 99m MIBI dual phase scan and ultrasonography are two common imaging techniques used for parathyroid localization. Concordance between two such localization studies increases success of parathyroid exploration. Concordance between MIBI and US images was noted in 54–61% in some earlier observations.^[14,15] We used MIBI scan and high resolution ultrasonography in sequential manor and recorded concordant results in 83.7% patients with cervical parathyroid lesions.

Dual phase protocol using technetium 99m MIBI is easy to perform and has efficacy to detect single-gland adenomas in 74–88% of occasions. However, the rate of correct localization drops down to 10–35% in multi-glandular lesions.^[16,17] Two potential covets in dual phase MIBI procedure are thyroid nodules and rapidly washing out variety of parathyroid adenomas. Thyroid nodules may concentrate MIBI and leads on to false-positive results.^[18] Adding single-photon emission computed tomography in initial and delayed phase of MIBI improves the accuracy but also escalates the cost.^[19] Overall prevalence of thyroid nodules is in about 9.6% in many geographical regions of the country.^[20] Thyroid nodules may concentrate the radiopharmaceutical and increase the chance of false positive MIBI images. However, on the contrary, we observed false negative results in these patients and so they probably belonged to rapidly washing out variety. Parathyroid adenoma may not retain the radiopharmaceutical and occasionally behave like thyroid nodule.^[21] The MIBI scan showed significantly high capability to identify correctly parathyroid lesions in our series even when they are related to superior pole of thyroid or placed ectopically. High serum level of PTH showed a positive influence of MIBI scan.

High resolution ultrasonography was complementary to MIBI scan and predicted anatomical features precisely. Ultrasonography helped to characterize coincident thyroid lesions. Surgeon performed ultrasonography prior to operation helped to avoid unnecessary dissection and reduced operation time.

We used Miami criterion^[22] in IOPTH monitoring and noted 97.84% sensitivity. This protocol has high accuracy and requires less blood draw.^[23] Persistent hypercalcemia occurred in 4 patients and IOPTH monitoring predicted true failure to decline in 3 patients. Excluding one patient with disseminated metastases from parathyroid carcinoma only two patients could have been cured by re-exploration. However, further exploration could not

locate an abnormal lesion in both cases and require higher imaging before further procedure. We feel that IOPTH monitoring does not add any additional advantage in patients with concordant imaging. In these situations persistent hypercalcemia warrants higher imaging since immediate further exploration is seldom successful.^[24] IOPTH monitoring is complementary when operating patients with discordant imaging.

There was no statistical difference between basal PTH level and preincision level but showed a trend toward higher values at the latter occasion. Since at the present protocol of two blood draws increases the cost of surgery by 7% (institutional audit), we propose single postexcision blood draw, but preferably after 15 min to avoid false negativity. All patients with false failure to decline showed true decline of PTH levels in the third blood draw after 30 min.

We feel that the major drawback of the study is retrospective design and lack of control group. The sample size appears adequate considering the rarity of the condition.

CONCLUSION

Dual phase technetium 99m MIBI parathyroid scintigraphy has good accuracy in symptomatic PHPT patients. There is relative low incidence of multi-gland pathology in symptomatic disease and successful parathyroidectomy is possible above 95% of patients with concordant images. IOPTH monitoring is very sensitive but unlikely to influence the outcome when concordant images are available.

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Conflicts of interest

There are no conflicts of interest.

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