Original Article

Focused Parathyroidectomy Using Accurate Preoperative Imaging and Intraoperative PTH: Tertiary Care Experience

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Abstract

Introduction: The cure rate after focused parathyroidectomy (FP) is dependent upon two critical adjuncts- concordant preoperative imaging and intraoperative parathyroid hormone (PTH), a technique which can reliably determine whether any other hyperfunctioning gland or glands are still present after resection of the lesion shown by imaging. We wanted to see the cure rate of FP by using these two adjuncts. We also sought to discern whether utilizing the central lab rapid PTH assay will lead to wider acceptance of this FP with intraoperative PTH in resource-constrained countries. This analysis was also undertaken to find out cost-effective way of doing intraoperative PTH by minimizing the samples for intraoperative PTH study. **Result:** Data were collected on 83 patients with sporadic primary hyperparathyroidism (PHPT) who underwent parathyroidectomy in two tertiary centers between '2009 and 2017'. A total of 75 patients had concordant imaging, while seven had discordant imaging. The sensitivity and specificity of intraoperative PTH in FP was 100%. All the 78 patients who had fall in intraoperative PTH (50%) at 10 min also had fall of more than 50% at 5 min except one patient (98.7%). **Conclusion:** We strongly advocate routine use of intraoperative PTH in all patients undergoing minimally invasive parathyroidectomy, as this adjunct offers maximum safety for the patient and confidence for the surgeon. Cost can be minimized by utilizing the central laboratory and reducing the number of samples.

Keywords: Focused parathyroidectomy, intraoperative PTH, preoperative imaging

Introduction

The intraoperative determination of parathyroid hormone (PTH) levels has become common practice in the surgical management of hyperparathyroidism. However, there is sparse literature on utility of intraoperative PTH, in patients with very high levels of PTH as there is not widespread acceptance of intraoperative PTH in developing countries due to cost constraints. The cure rate after focused parathyroidectomy (FP) is dependent upon two critical adjuncts- concordant preoperative imaging and intraoperative PTH a technique which can reliably determine whether any other hyperfunctioning gland or glands are still present after resection of the lesion shown by imaging. We wanted to see the cure rate of FP by using these two adjuncts. We also sought to discern whether utilizing the central lab rapid PTH assay will lead to wider acceptance of this FP with Intraoperative parathyroid hormone (IOPTH) in resource-constrained countries.

The criteria used for IOPTH is always a matter of discussion. We know that an ideal criterion should identify all patients with multiglandular disease while reducing the number of unnecessary bilateral neck exploration. The stricter criteria lead to more number of false explorations, whereas less strict criteria lead to missing more multiglandular disease[1,2] This analysis was also undertaken to find out cost-effective way of doing IOPTH by minimizing the samples for IOPTH study.

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Materials and Methods

Data were collected on 83 patients with sporadic PHPT who underwent parathyroidectomy between '2009 and 2017 by two endocrine surgeons. PTH samples were collected at different time points: preincision, preexcision, and then at 5, 10, and 15 min after excision of suspected abnormal parathyroid gland(s) and they were analyzed by the chemiluminescence method in the central lab [Figure 1]. In one center we used

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IMMULITE and IMMULITE 1000 system 'Turbo Intact PTH' automated analyzer (Diagnostics Products Corp., Los Angeles, CA, USA) based on a solid phase two site chemiluminescent enzyme labeled immunometric assay according to the manufacturer's specifications.

The second center used Advia centaur, Siemens with chemiluminescence method in central lab for measuring the intact PTH level intraoperatively.

The first rapid or intraoperative assay was proposed by the same group Nussbaum and colleagues that developed the intact PTH IRMA assay (immunoradiometric assay). By altering sample and reagent volumes and incubation temperature, they developed an assay with an incubation time of 15 min—compared with the 22 h for the unaltered assay.[3]

Preoperative imaging

Our preoperative imaging protocol included high-resolution Ultrasonography (USG) and SestaMIBI scan. The imaging was labeled as concordant only if they matched for side, site, and number. The high-resolution ultrasound of neck was done by dedicated radiologist of the two institutes. If the patient came with an outside report, it was always reviewed by radiologist at the institute. The ultrasound was also repeated by the surgeon in the operating room before surgery in order to mark the incision for mini incision FP. Concordant imaging [Figure 2] means identifying same gland on both ultrasound and SestaMIBI scan. Nonidentification of any gland on both is called negative localization. Discordant imaging is when there is difference in the gland localized on both imaging. It can be either discordant for side (left or right) [Figure 3a] or gland position i.e., site [Figure 3b] (superior or inferior gland) or for both side and site [Figure 3c] as well as discrepancy in number of glands shown by two imaging modalities [Figure 3d].

Protocol for IOPTH testing

A baseline blood sample is obtained from a peripheral intravenous catheter. The sample is transferred into an Ethylenediaminetetraacetic Acid (EDTA) vacutainer tube, mixed, and centrifuged, and 200 m L plasma is incubated.

Figure 1: Chemiluminescence machine in central lab

After incubation at 45°C the light output is measured in a luminometer after initiation of the chemiluminescent reaction. The elapsed time from blood sample to hormone value is 12–14 min. Intact PTH has a half-life of less than 5 min and as other glands are suppressed plasma PTH levels decline rapidly after all hypersecreting parathyroid tissue has been removed. Accordingly, a postresection plasma PTH level is measured 5 min after tumor extirpation. A 50% fall from the baseline level indicates an adequate resection.

Surgical cure was defined as a drop of greater than 50% in PTH level at 10 min from the highest of the baseline preincision or preexcision value (Miami criteria). Patients were clinically cured if they became normocalcemic postoperatively and remained so for 6 months. The data were analyzed to determine how accurately IOPTH predicted success or failure of parathyroidectomy.

Surgical procedure

The surgical approach used in parathyroid surgery is bilateral neck exploration (BNE), unilateral neck exploration (UNE), and focused or limited parathyroidectomy.

BNE is the gold standard and includes visualization of all four glands and removal of the offending gland. If any of the gland is not seen then we have to search at embryological places.

UNE is visualizing the glands on one side. Focused or limited parathyroidectomy is removal of the offending gland without visualization or search for other glands.

Focused or limited parathyroidectomy can be performed by various incision that is either small incision right over the offending gland [Figures 4 and 5a, b] or conventional incision. FP is attempted after we have a concordant imaging on preoperative evaluation. Patients with concordant imaging underwent FP. Patient with discordant imaging underwent bilateral or unilateral exploration. Patients with concurrent

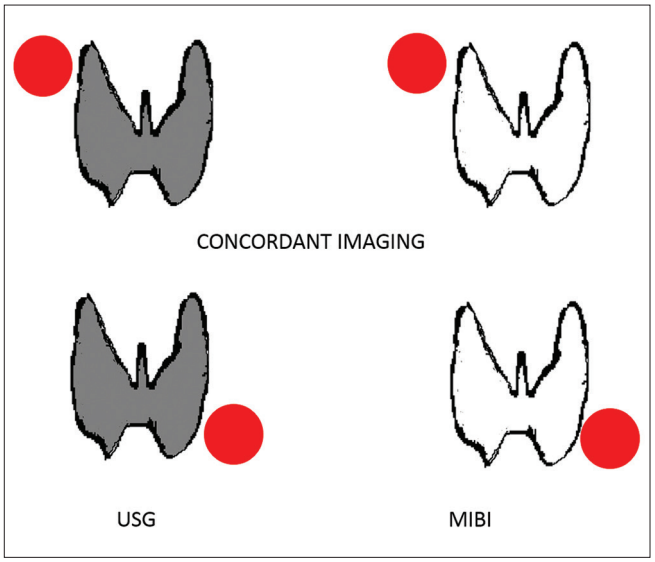

Figure 2: Concordant imagining: Both MIBI and USG points to the same offending gland

thyroid nodule also underwent conventional exploration. We defined FP as a procedure which utilizes a small incision (<2 cm), minimal dissection, and removal of the single adenoma without making a deliberate attempt to dissect or visualize the other normal gland on that side. Briefly the procedure involved making a small incision [Figure 4], either central or oblique, dilatation of the space with index finger, and dissecting the space between the strap muscles and the Sternocleidomastoid (SCM). Once the adenoma is visualized it is bluntly dissected out from the surrounding tissues using a small peanut, taking care to keep hugging the adenoma during dissection to avoid injury to the RLN.

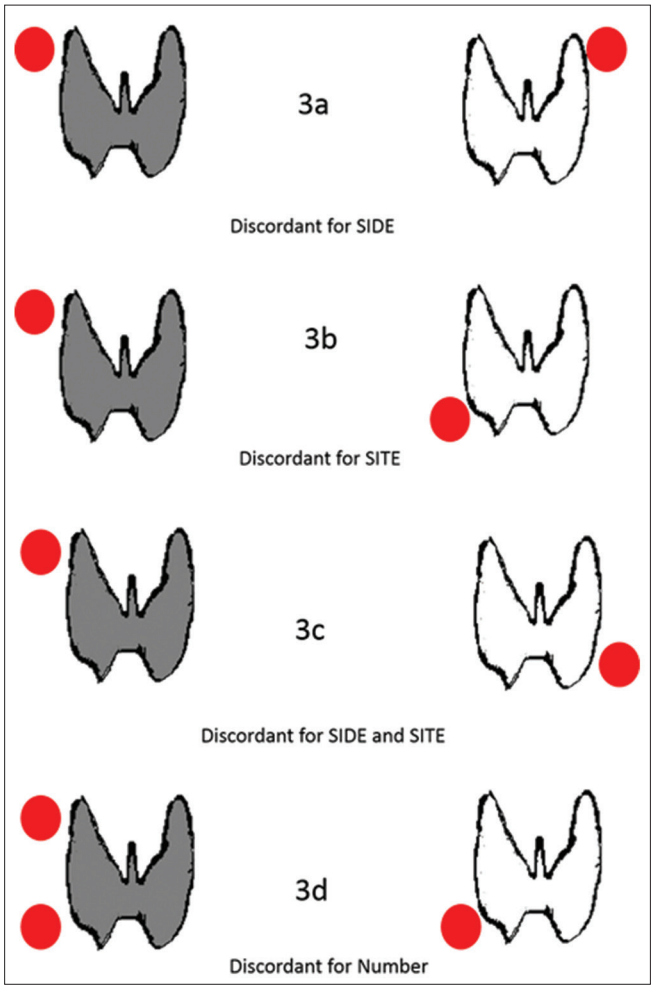

Figure 3: Figure depicts discordant imaging. (a) Discordant for side (USG shows right superior and MIBI shows left superior). (b) Discordant for site (USG: Right superior, MIBI: Right inferior). (c) Discordant for side and site (USG: Right superior, MIBI: Left inferior). (d) Discordant for number (two lesions of USG and one on MIBI)

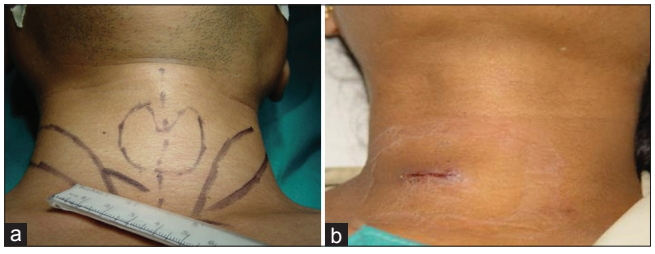

Figure 5: (a) 2.5 cm lesion over the gland. (b) Postoperative scar

Results

A total of 83 patients underwent parathyroidectomy with intraoperative PTH monitoring in two centers operated by two surgeons. The demographic data are shown in Table 1.

Preoperative Sestamibi parathyroid scan and ultrasound was done in all cases except one because of pregnancy in which only ultrasound was used. A total of 75 patients had concordant imaging, while 7 had discordant imaging. And 57 underwent focused, whereas 9 underwent unilateral and bilateral exploration [Figure 6]. Also, six out of nine patients who underwent BNE has intraoperative suspicion of parathyroid carcinoma; however, none turned out to be carcinoma in final histopathology. Out of the three patients who underwent bilateral neck exploration one had concomitant PTC, one was reoperative, and third one suspicious of jaw tumor syndrome. The operative results are shown in line Figures 6 and 7. The sensitivity and specificity of intraoperative PTH in FP was 100% (TP/TN mentioned in Tables 2 and 3). All the 78 patients who had fall

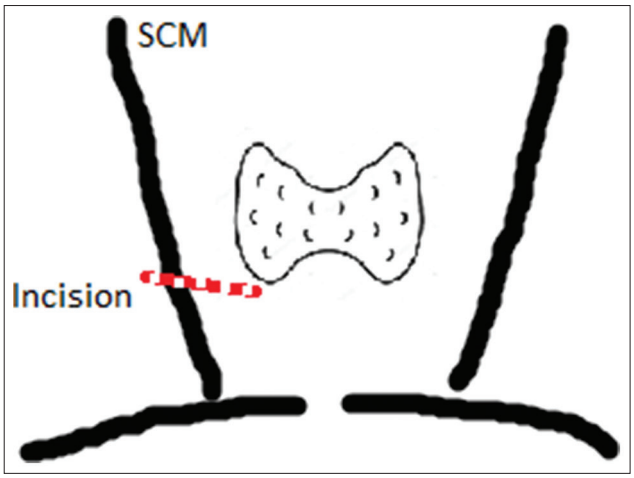

Figure 4: Line diagram showing the placement of oblique incision for FP

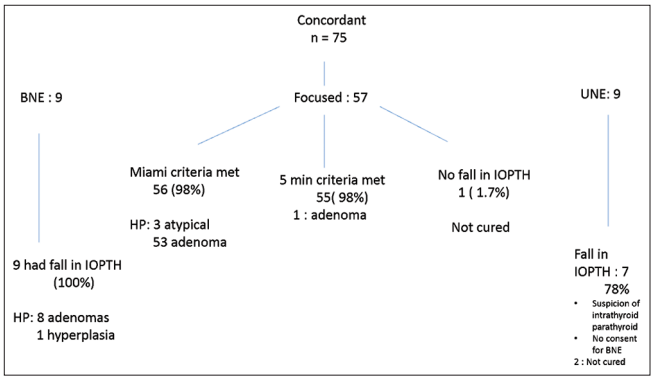

Figure 6: Operative chart of patients with concordant imaging

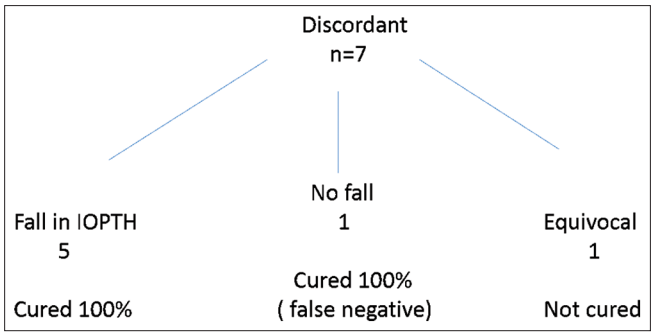

Figure 7: Operative plan of patients with discordant imaging

in intraoperative PTH (50%) at 10 min also had fall of more than 50% at 5 min except one patient (98.7%).

Discussion

PHPT is not an uncommon disorder. The commonest cause of PHPT is a single gland adenoma present in 80–85% of patients, followed by hyperplasia in 15–20% and carcinoma in less than 1%. The management also evolved with first parathyroidectomy performed by Mandl in 1924[4] with visualization of all the four glands and excision of single enlarged gland. As the clinical spectrum of disease evolved from severe symptomatic to asymptomatic disease, the surgical approach also evolved from bilateral neck exploration to focused approach with evolution of various preoperative investigations along with adjuncts.

For FP it is mandatory to get preoperative imaging, i.e., one anatomic and one functional. The goal of preoperative imaging for hyperparathyroidism is to identify the location of abnormal parathyroid tissue as precisely as possible. Accurate preoperative imaging techniques, such as technetium (99mTc), SestaMIBI scan, and US can reduce unnecessary search and enable minimal invasive surgery. Technetium (99mTc) SestaMIBI scan is the imaging of choice with sensitivity ranging from 54% to 88%.[5-8] The high-resolution ultrasound has sensitivity ranging from 59 to 89%.[5,6] The sensitivity of combined imaging is more than individual test. The success rates of FP following concordant imaging are much more than when FP is done in patients with only one positive imaging. In our series 57 underwent FP out of 75 patients with concordant imaging. There were various reasons for nine patients who underwent BNE in spite of concordant imaging (six had intraoperative suspicion of parathyroid carcinoma, one patient had preoperative diagnosis of PTC, one was reoperative, and one had suspicion of jaw tumor).

However, about 5% of patients with concordant imaging will have unexpected intraoperative findings like adenoma in different location and therefore intraoperative PTH remains an important adjunct to ensure removal of all the hyperfunctioning glands.[9]

Excellent outcome after intraoperative PTH-guided parathyroidectomy

Intraoperative PTH is the most commonly used adjunct with FP. Numerous large studies have documented excellent cure rates after IOPTH-guided parathyroidectomy. In the series by Chen *et al*.[10] they divided patients in two groups, one without intraoperative PTH and the other with intraoperative PTH monitoring. In the group without intraoperative PTH (10%) were still hypercalcemic postoperatively owing to additional unidentified hyperfunctioning parathyroid glands. In contrast in group with intraoperative PTH10% did not have an adequate reduction of intraoperative PTH levels and underwent bilateral exploration with resection of additional parathyroid. Of these, 18 patients, 9 had double adenomas, and 9 had 3 or 4 gland hyperplasia. All patients in intraoperative PTH group were subsequently cured. The authors concluded that intraoperative PTH testing allowed intraoperative recognition and resection of additional hyperfunctioning parathyroids missed by preoperative imaging.

Another advantage of using IOPTH is its utility in suggesting presence of double adenomas even when the preoperative imaging detected a single adenoma. In the study by Haciyanli *et al*.[11] the combined accuracy of USG, MIBI, and IOPTH assay in predicting a double adenoma was 80%. However, there are numerous criteria to define cure when IOPTH is used. A number of other criteria are mentioned in literature like the Vienna criteria, 5 min criteria, Halle criteria, and the residual criteria by Libutti *et al*.[12-16] Most commonly followed criteria for defining cure is using a decline of ≥50% within 10 min after excision of the gland during surgery for PHPT (Miami criteria).[17] Because of cost constraints in India where intraoperative PTH is used only in selected centers

Table 1: Demographic data

Number	Value $n=83$
Male/Female	28/55
Mean age (years)	43±15
Mean duration of symptoms (months)	43±38
Peak serum calcium (mg/dl)	12.4±1.8
iPTH (pg/ml)	535±603
Alkaline Phosphatase (IU/L)	626±936
Weight (Milligrams)	3986±5481
Size (cm)	2.6±0.99

Table 2: Sensitivity and specificity of IOPTH

Patients (IOPTH)	83
True positive	78
True negative	3
False negative	1
Equivocal	1

Table 3: Sensitivity and specificity of IOPTH in Focused parathyroidectomy

Focused (IOPTH)	57
True positive	56
True negative	1

as routine adjunct; therefore, a method to reduce time and financial burden is always sought for. Two modifications can help in bringing down the cost of IOPTH. One way could be to reduce the number of samples needed to define cure. Hence, we looked at our patients the 5 min criteria can be used in our set of patients. We found that all the 78 patients who showed fall in intraoperative PTH by Miami criteria also showed curative fall even at 5 min except one patient (98.7%). This result is in contrast to the results by Riss *et al*.[14] in which the 5 min criteria was true only in 71% of patients. This difference in results can be due to very high mean PTH levels in our patients as compared to their set of patients (mean PTH 535 pg/ml as compared to 131.8 pg/ml). The second modification that could be made is the use of central laboratory for quick results. The first commercial IOPTH assay was a tabletop analyzer that was placed on a portable cart for on-site operation in or near the surgical suite, but a dedicated technologist was needed to perform pretesting instrument calibration and on-site operation; therefore, the cost per test was significantly higher when the testing volume was low. Rapid PTH assays were subsequently added to standard immunoanalyzers and could be performed at central laboratories. These rapid intraoperative PTH assays have good analytic correlations with standard PTH assays and diagnostic agreement with respect to patient outcomes[18] Cost, total turnaround time (TAT), and staffing are three major factors to consider when selecting the optimal testing format.

The cost of setting up intraoperative PTH testing at a central laboratory is minimal, the reagent cost is low, and laboratory personnel can perform intraoperative PTH testing at scheduled times (and may be able to concurrently perform other tests).[19-21] On-site intraoperative PTH monitoring is preferred if the laboratory is not close to the surgical site and transporting intraoperative PTH samples requires a TAT greater than 45 min.

Long-term results

Patients were regarded as clinically cured if they became normocalcemic postoperatively and remained so for 6 months. This is the traditional definition of operative success. In our study, 56 of 57 patients who underwent FP showed curative fall in IOPTH and clinical cure. One patient who did not showed fall in IOPTH was not cured. However, BNE could not be performed in this patient since the procedure was being performed in local anesthesia (pregnancy).

Critics have expressed concern that enlarged hyper functioning glands may be left in situ, leading to higher failure rates in terms of persisting and recurrent disease.[22] This concern is largely based on studies that have shown, during bilateral exploration, a number of patients with a remaining enlarged gland after the hyper functioning gland had been excised (with a significant decline in IOPTH level). However, these studies have overestimated Multiglandular disease (MGD). If such predicted rates of missed MGD were correct, a higher 15–30% recurrence rate would have been appreciated instead of the 3% rate of recurrent disease from this long-term study.[23] Not only excellent short-term results after MIP with IOPTH monitoring, long-term results after limited surgery has also been shown. Lew and Irvin *et al*.[23] reported 164 patients with a mean Follow up period (FUP) of 83 months. There were only four late recurrences. The authors concluded that in patients 10 years after treatment, IOPTH-guided MIP does not fail to identify MGD and showed that the various sized parathyroid glands left in-situ do not cause higher recurrence rates.

Conclusion

We strongly advocate routine use of IOPTH in all patients undergoing MIP, as this adjunct offers maximum safety for the patient and confidence for the surgeon. Utilizing the central laboratory for quick results and just taking one postoperative sample at 5 min is likely to bring down the cost involved in IOPTH and lead to liberal use in developing countries.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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