

Intraoperative parathyroid hormone assay-cutting the Gordian knot

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ABSTRACT

Background: Hyperparathyroidism is treated by surgical excision of the hyperfunctioning parathyroid gland. In case of adenoma the single abnormal gland is removed, while in hyperplasias, a subtotal excision, that is, three-and-a-half of the four glands are removed. This therapeutic decision is made intraoperatively through frozen section evaluation and is sometimes problematic, due to a histological overlap between hyperplasia and the adenoma. The intraoperative parathyroid hormone (IOPTH) assay, propogated in recent years, offers an elegant solution, with a high success rate, due to its ability to identify the removal of all hyperfunctioning parathyroid tissue. **Aim:** To study the feasibility of using IOPTH in our setting. **Materials and Methods:** Seven patients undergoing surgery for primary hyperparathyroidism had their IOPTH levels evaluated, along with the routine frozen and paraffin sections. **Results:** All seven patients showed more than a 50% intraoperative fall in serum PTH after excision of the abnormal gland. This was indicative of an adenoma and was confirmed by histopathological examination and normalization of serum calcium postoperatively. **Conclusion:** The intraoperative parathyroid hormone is a sensitive and specific guide to a complete removal of the abnormal parathyroid tissue. It can be incorporated without difficulty as an intraoperative guide and is superior to frozen section diagnosis in parathyroid surgery.

Key words: Frozen section, intraoperative parathyroid hormone assay, parathyroid adenoma, parathyroid hyperplasia

INTRODUCTION

The incidence of primary hyperparathyroidism (PHPT) is increasing due to the widespread use of multichannel analyzers. The parathyroid lesions are mostly early adenomas, and fewer parathyroid hyperplasias. These two entities have overlapping histological features,^[1] which sometimes preclude a definitive frozen section diagnosis.

The parathyroid hormone (PTH) is produced exclusively by the parathyroid glands. Hyperplasias, adenomas, and carcinomas, cause hypersecretion of this hormone and elevated serum PTH. The half-life of the PTH is short,

three-to-five minutes, and excision of the parathyroid tissue is followed by a rapid fall in serum levels. PTH assays, with a turnaround time of 15-20 minutes, have made intraoperative PTH analysis a reality in various centers.^[2]

Endocrine surgeon, George Irwin, is credited with first utilizing this phenomenon in parathyroid surgery. Successful surgery is determined by a drop of over 50% in the intraoperative plasma parathyroid hormone level when compared with the preoperative value.

A short study of seven cases of parathyroidectomy with the use of intraoperative PTH is hereby presented.

MATERIALS AND METHODS

The intraoperative parathyroid hormone (IOPTH) assay was performed in seven patients undergoing parathyroidectomies for primary hyperparathyroidism. The blood sample was drawn from a peripheral vein 10 minutes after surgical excision of the abnormal gland and sent to the laboratory. Care was taken to prevent dilution with

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intravenous fluids. The PTH levels were estimated by the use of a rapid Electrochemiluminescence immunoassay (ECLIA) on the Cobas 6000 combi analyzer. The excised gland was also sent for frozen section examination.

The Elecsys assay for determining intact PTH employs a Sandwich Test Principle, in which, the biotinylated monoclonal antibody reacts with the N-terminal fragment (1-37) of the parathyroid hormone and a monoclonal antibody labeled with a ruthenium complex reacts with the C-terminal fragment (38-84). The antibodies used in this assay are reactive with epitopes in the amino acid regions 26-32 and 37-42.^[3]

RESULTS

The results are tabulated in Table 1. In case No. 1, multiple frozen section examinations were done for 'suspected' nodules excised from different areas, including the mediastinum. The nodules excised were lymph nodes. A hemithyroidectomy for goiter, done in the same sitting, revealed that the parathyroid adenoma was ectopically located within the left lobe of the thyroid. The intraoperative PTH showed a fall from 128.8 to 5.8 mgm%, indicating removal of all hyperfunctioning parathyroid tissue. The postoperative period was uneventful and both the serum PTH and calcium levels normalized.

In the next two and the last three patients, the frozen section revealed an enlarged hypercellular parathyroid gland

consistent with either adenoma or hyperplasia. The IOPTH values showed a fall of more than 50%, confirming removal of all hyperfunctioning tissue, and therefore, confirming an adenoma. No further exploration was done, and no second gland was excised.

In the fourth patient, only IOPTH was done and frozen section examination was not performed.

The IO-PTH dropped to >50% in all the seven cases, with an average intraoperative fall of 73%. The operative time was increased by 15 minutes on an average. In all seven patients, the final histopathology on the paraffinized tissue was consistent with a parathyroid adenoma and correlated with the postoperative normalization of both PTH and calcium values.

DISCUSSION

Primary hyperparathyroidism is most often caused by a single adenoma, often small in size and difficult to localize with imaging techniques. Diffuse hyperplasias account for only 9% of all patients with PHPT. In secondary and tertiary hyperparathyroidism, the diagnosis is self evident,^[4] due to the underlying disease.

Hypercalcemias seen in malignancy can be due to the PTH-related plasma protein (PTHrP). This protein is not detected by the technique used for the PTH assay. Serum PTH levels are, conversely, low in paraneoplastic hypercalcemia related to PTHrP.^[5]

Table 1: Comparison of IOPTH assays, frozen and paraffin section results

Age (years); Sex	Preop PTH pg/ml	Intraop PTH (pg/ml) 10 Minutes after excision	%Drop	Frozen section samples received	FS Diagnosis	Total no. of frozen sections received	Gross size	Final diagnosis	Follow-up
41, F	125.8	5.58	77.5	Upper-mediastinal nodule Lt paratracheal tissue with two nodules. Pre-tracheal, and superior mediastinal tissue. Lt hemithyroid	Lymph node Lymph nodes Lymph Nodes Intrathyroid parathyroid adenoma	Four	2.5 cm	Intra-thyroid Parathyroid adenoma	Subsequent levels of PTH and calcium were within normal limits, confirming no residual disease and successful excision of a solitary parathyroid adenoma in all cases
76, F	102	24	75.5	Single nodule	Superior parathyroid	One	1.7 cm	Parathyroid adenoma	
52, M	400	61	84.7	Single nodule	Lt Inferior parathyroid	One	2.5 cm	Parathyroid adenoma	
46, M	1456	726	50.2	No FS examination	Lt Inferior parathyroid	Nil	1.5 cm	Parathyroid adenoma	
55, F	197	34	83	Single nodule	Lt lower Parathyroid	One	1.8 cm	Parathyroid Adenoma	
74, M	150	25	83	Single nodule	Lt lower Parathyroid	One	1.5 cm	Parathyroid Adenoma	
58, F	346	130	63	Single nodule	Lt parathyroid	One	3.7 cm	Parathyroid adenoma	

PTH: Parathyroid hormone, IOPTH: Intraoperative parathyroid hormone, FS: Frozen section

The standard surgical technique for hyperparathyroidism is a bilateral neck exploration to identify the parathyroid adenoma and the other three normal glands. The suspected adenoma and one more 'normal' gland are excised and sent for frozen section examination. Cellularity and size are compared. If one is hypercellular and the other normocellular, the hypercellular gland is an adenoma and surgical treatment is complete. If both are hypercellular the diagnosis is hyperplasia, and subtotal parathyroidectomy is performed, that is, three-and-a-half glands are removed. Histologically, hypercellularity is defined as replacement of the normal glandular fat by parathyroid cells followed by gradual gland enlargement. When it is understood that normal aglandular fat varies from 17 to 50% and normal glands vary in size from 3-6 mm, the problems encountered in frozen section diagnosis become evident.

The additional pitfalls are:^[6]

- (1) Although parathyroid glands usually number from four to five, they can range from two to twelve. Thus, removal of two glands could mean loss of all parathyroid tissue and excision of three-and-a-half glands in hyperplasia could still leave several hyperfunctioning glands
- (2) Fifteen to twenty percent of the parathyroid glands are often ectopically located, for example, in the mediastinum and intrathyroid, and this causes difficulty in intraoperative identification
- (3) Thyroid follicular adenomas, lymph nodes, and the like, can show freezing artifacts leading to misidentification as parathyroid adenomas and vice versa.

On the other hand, IOPTH is a specific and sensitive guide, as a 50% drop in serum hormone levels signals removal of all hyperfunctioning parathyroid tissue.

The chances of operative failure are reduced.^[7] Procedures like minimally invasive parathyroidectomy, with excision of only a single adenoma are slowly replacing the traditional four gland bilateral exploration, leading to a decrease of the surgical field, reduced hospital stay, and improved cosmesis.^[8]

Surgical failures^[9] in IOPTH can be due to excessive pre-excision manipulation, leading to a falsely elevated initial reading, false post-excision drop in levels, or rarely, due to a dominant tumor suppressing other tumors in the multiple endocrine neoplasia (MEN) syndrome.^[10]

CONCLUSION

The IOPTH assay is a useful test in parathyroid surgery because of its unique ability to,

- (1) Identify the complete removal of hyperfunctioning tissue. The intraoperative persistence of elevated

PTH would indicate residual hyperfunctioning tissue and signal the need for further exploration and thus operative failure is prevented

- (2) Facilitate minimally invasive parathyroidectomy for single parathyroid adenomas, which in turn improves the cost-effectiveness, duration of hospital stay, and cosmetic outcome.

Following implementation of this test, parathyroid excision in this institute has had a zero surgical failure rate, reduced the number of frozen section requests, and decreased the field of operation, with improved cosmesis to the patient.

It is agreed that the successful use of IOPTH in the seven cases presently reported is a small number, but as the validity of this procedure is corroborated in several institutes worldwide, it was thought important to convey to pathologists and surgeons alike, the feasibility of conducting IOPTH in their respective institutes in this country and avail of its multiple advantages.

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