Use of Intraoperative Parathyroid Hormone Assay

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Introduction

The availability of the rapid, intraoperative measurement of PTH (IOPTH) has changed the surgical approach to primary hyperparathyroidism (PHPT). Although bilateral cervical exploration with identification of all four parathyroid glands remains the standard to which all other surgical approaches are compared, the majority of patients undergoing surgery for PHPT in the United States undergo a less extensive exploration, limited to the removal of the single adenoma identified on preoperative imaging. This approach, frequently referred to as "minimally invasive parathyroidectomy" (MIP), is more accurately described as focused or single-gland exploration. MIP is not a surgical technique defined by the size of the incision or whether the procedure is performed endoscopically, robotically, or with video assistance. Rather it is a concept based on the fact that 80–85 % of patients with PHPT have a single adenoma and that while the location of this adenoma can be identified by preoperative imaging in most patients, preoperative imaging can only predict the presence of multiple hyperfunctioning parathyroid glands in 50 % of those patients in whom they occur. Based on these tenets, MIP is performed by removing the hyperfunctioning parathyroid gland identified on preoperative imaging and then measuring IOPTH. If IOPTH falls adequately, the procedure is terminated without identifying the remaining parathyroid glands. If all patients with PHPT had single adenomas or if preoperative imaging had a high sensitivity for the identification of those patients with multiple hyperfunctioning parathyroid glands, IOPTH would not be necessary. The crucial role of IOPTH is to predict the presence of additional hyperfunctioning parathyroid glands in those few patients, about 7 %, in whom imaging identifies one abnormal gland but who in fact have multiglandular disease. IOPTH does not necessarily confirm that parathyroid tissue that is removed is normal or abnormal. Rather it confirms that no residual hyperfunctioning parathyroid tissue remains in the neck.

History

The radioimmunoassay of PTH was first described by Berson, Yalow, and their associates in 1963. In 1988, Nussbaum et al. demonstrated that IOPTH fell to 40 % of baseline values within 15 min of the removal of a parathyroid adenoma and suggested that the "Intraoperative measurement of PTH by modification of this IRMA may complement surgical skill and histopathologic information and has the potential for providing guidance regarding the extent of neck exploration necessary for determining surgical care of

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D.J. Terris, M.C. Singer (eds.), *Minimally Invasive and Robotic Thyroid and Parathyroid Surgery*,
DOI 10.1007/978-1-4614-9011-1_15,

hyperparathyroidism." Technical advances through the years have made the rapid intraoperative measurement of PTH by automated equipment either in the operating suite or in the central chemistry laboratory feasible. Dr. George Irvin, at the University of Miami, deserves recognition as the surgeon who was most responsible for demonstrating the clinical usefulness of IOPTH. Interestingly, in his initial report, IOPTH was used to decrease the failure rate in patients undergoing bilateral exploration, not to permit limited exploration. In multiple publications over the next two decades, his group has demonstrated that IOPTH could be used successfully to perform MIP with excellent immediate and long-term cure rates. Many other authors have confirmed his findings.

Technical Aspects

While it is convenient and expeditious to measure IOPTH in the OR suite, successful programs can function measuring IOPTH in the central chemistry lab if systems are developed to assure the rapid delivery of samples to the lab and the direct reporting of results to the OR. IOPTH values should be available within 30 min of being drawn and many systems can generate results in less than 20 min. Blood samples for IOPTH can be drawn from either an indwelling peripheral venous or intra-arterial cannula. We find the use of the jugular vein for routine sampling to be cumbersome, particularly through a small incision. In addition, the incision cannot be closed until the final sample is drawn. A baseline sample should be drawn as soon as the patient enters the operating room. In many patients, this intraoperative baseline is quite different from the most recent preoperative PTH. This sample should be obtained before the incision is made or the neck is palpated. Palpation of parathyroid adenomas can result in a sudden increase (spike) in IOPTH that can confound the interpretation of subsequent IOPTH values. Induction of general anesthesia may do this as well. The timing of subsequent IOPTH samples varies among institutions. Because the half-life of the intact PTH molecule is less than 2 min in most patients and almost never longer than 4 min, samples drawn 10 min after the hyperfunctioning gland is removed will usually demonstrate successful resolution of hyperparathyroidism. The decay curve is not simple first- or second-order kinetics, however, and IOPTH may take substantially longer to fall into the normal range when the baseline value is unusually high. It is important, and our practice, to obtain a sample at the time of excision of the enlarged parathyroid. Intraoperative manipulation of a hyperfunctioning parathyroid can result in a dramatic spike in IOPTH. Failure to recognize this may mislead the surgeon into thinking that IOPTH has not fallen adequately if samples are obtained only at 5 or 10 min after excision. In Fig. 15.1 it is demonstrated that if the "at excision" sample is not obtained, IOPTH levels at 5 and 10 min can suggest that additional hyperfunctioning parathyroid tissue is present and leads to unnecessary additional exploration. Another potential benefit of the "at excision" sample is that in some patients IOPTH has already decreased to an acceptable level, probably due to devascularization of the parathyroid, before it is actually removed, permitting early termination of the procedure. We usually draw samples at 15 and 20 min as well. While in many patients these prove unnecessary, in those patients in whom IOPTH decreases more slowly than normal or in whom there is an IOPTH spike at excision, substantial delay can result if additional samples are not drawn until the results of earlier samples are obtained.

There is no universal agreement on what constitutes an adequate decrease in IOPTH to assure cure. George Irvin and his associates rely on a 50 % decrease at 10 min from either the baseline or "at excision" IOPTH. Many surgeons feel uncomfortable terminating the procedure before the IOPTH has decreased more than 50 % from the baseline and into the normal range. Other permutations of this, all based on a percentage decrease at a set time interval, have been proposed. In most patients, IOPTH either falls dramatically after removal of the hyperfunctioning gland or falls hardly at all, making the decision to proceed with further exploration relatively simple. It should

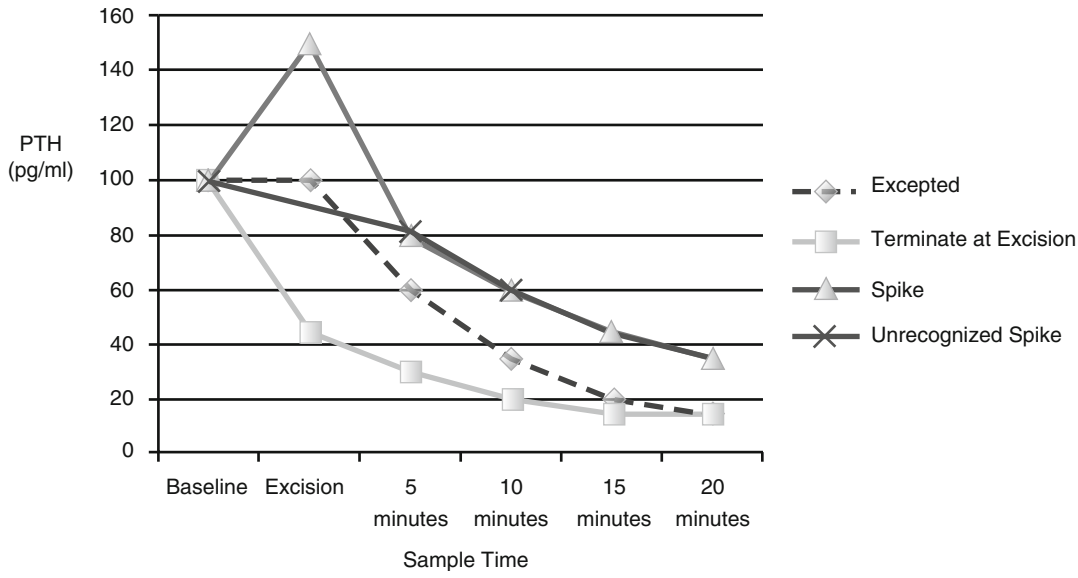

Fig. 15.1 Patterns of IOPTH decrease

also be noted that in some patients the baseline IOPTH is actually in the normal range. Even in these patients substantial decreases in IOPTH are usually observed following removal of the hyperfunctioning parathyroid(s).

Early in my experience, it became apparent that patients whose decrease in IOPTH level barely met the standard criteria had a higher incidence of persistent hyperparathyroidism postoperatively compared with those in whom the IOPTH decrease was dramatic. Requiring a greater decrease in IOPTH may result in fewer cases of persistent hyperparathyroidism after surgery but results in an increase in the number of unnecessary bilateral explorations. In a retrospective analysis of 194 patients, we found that persistent hyperparathyroidism after surgery almost always occurred in those patients whose final IOPTH was >40 pg/ml (although in all patients IOPTH decreased by at least 50 % and into the normal range) regardless of the percentage decrease from baseline. It would appear that the absolute final value of IOPTH is more predictive of success than the percentage decrease.

Some authors have suggested that MIP can be performed with a high success rate in many patients without the time and expense of IOPTH measurement. They argue that in a patient who only has a solitary adenoma that is localized by appropriate imaging, measurement of IOPTH is unnecessary. Kebebew et al. proposed a simple scoring system based on the results of preoperative sestamibi scans, ultrasonography, serum calcium level, and PTH that was 99 % accurate in predicting the presence of a single hyperfunctioning parathyroid. Others have suggested that the presence of concordant sestamibi and ultrasonography studies reliably predicts single-gland hyperparathyroidism and that measurement of IOPTH is not necessary in these patients. Our own experience differs from this. In patients with concordant sestamibi and ultrasonographic images demonstrating a solitary adenoma, 8 % of patients had additional enlarged hypercellular parathyroid glands found during further exploration performed because the decrease in IOPTH did not meet our criteria for successful surgery.

Other authors have criticized the entire concept of MIP based on IOPTH or radio guidance (see Chap. 5). Siperstein and his colleagues at the Cleveland Clinic have reported the results of their practice of measuring IOPTH while performing bilateral parathyroid exploration on all patients. In patients with preoperative imaging identifying a single adenoma and in whom IOPTH met the usual criteria for successful surgery following

removal of the imaged parathyroid, 16 % were found to have additional enlarged hyperfunctioning parathyroid glands on bilateral exploration. This observation is difficult to reconcile with the results of many large series of focused, single-gland explorations in which the failure rate is only about 2 %. It would appear that either many patients will recur over time or that the enlarged, hypercellular parathyroid glands identified by Siperstein and his colleagues are of no clinical (and functional) significance.

There is another possible explanation for this observation. It has been well established that at least 15 % of patients whose calcium returns to normal after apparently successful parathyroidectomy have persistently elevated PTH postoperatively. In many patients, this is due to vitamin D deficiency or mild secondary hyperparathyroidism due to hypocalcemia. In some, however, the persistently elevated PTH is associated with normal vitamin D levels and calcium in the high normal range. These patients may indeed have mild persistent primary HPT and have been demonstrated to have a relatively high incidence of recurrent HPT with hypercalcemia. It is possible that those patients with additional enlarged, hypercellular parathyroid glands identified by Siperstein (which would not have been removed if exploration was terminated after an adequate decrease in IOPTH) may be responsible for this phenomenon.

Norman, in Tampa, was an early and enthusiastic advocate of MIP. Rather than assess the adequacy of parathyroidectomy by IOPTH, he used radio guidance to demonstrate that all hyperfunctioning parathyroid tissue had been removed. In a recent publication, he reported that long-term follow-up of his patients who had undergone limited exploration revealed a 6 % failure rate compared to a 99.4 % cure rate in those who had bilateral exploration. He concludes from this observation that limited exploration has an unacceptable high failure rate and should be abandoned. An alternative interpretation of his data, however, is that radio guidance is not an adequate substitute for IOPTH and that the difference in long-term outcome observed comparing limited with bilateral exploration would not have occurred had he determined the adequacy of surgery by IOPTH.

It will require many years of careful follow-up to confirm that MIP results in long-term cure rates of hyperparathyroidism comparable to bilateral exploration. Most studies published to date certainly support this. It is not adequate to follow serum calcium alone. At least 13 % of patients undergoing surgery for HPT are normocalcemic. In recent years in our practice, that figure has reached 19 %. These patients have significant clinical disease. Return of postoperative calcium levels to the normal range without knowledge of PTH levels is not a guarantee that the patient does not have mild persistent hyperparathyroidism. Serum calcium and PTH should be followed postoperatively, and in those patients with persistently elevated PTH, bone densitometry should be performed periodically. Lack of improvement or increase of bone loss would suggest that persistently elevated PTH, even in the presence of normocalcemia, is clinically significant. At the present time, there is insufficient data to suggest that MIP should be abandoned.

Other Uses of IOPTH

The measurement of IOPTH can help the surgeon in clinical situations other than MIP. There are many patients in whom bilateral exploration is necessary. Patients with inconclusive preoperative imaging or patients in whom imaging suggests multiple hyperfunctioning parathyroid glands are not candidates for MIP. Even the most experienced parathyroid surgeons can have difficulty differentiating normal from minimally enlarged, hyperfunctioning parathyroid glands, and persistent hyperparathyroidism can occur after bilateral exploration. Multiglandular parathyroid hyperplasia is not necessarily symmetrical. The presence of one obviously enlarged parathyroid does not mean that some of the smaller, relatively normal appearing glands are not hyperfunctioning. Frozen section biopsy of minimally enlarged parathyroid glands jeopardizes their viability. In addition, pathologists may not be able to differentiate normal from hypercellular parathyroid

glands on frozen section when given a very small biopsy sample. When performing a bilateral exploration, persistence of IOPTH elevation following removal of an obviously enlarged parathyroid should prompt the removal or biopsy of additional parathyroid glands that appear relatively normal.

Conversely, while the goal in bilateral parathyroid exploration is to identify all four parathyroids, this is not always possible. If during the exploration an enlarged gland(s) is identified and one or more of the remaining glands cannot be identified, a decrease of IOPTH predictive of cure permits the surgeon to terminate the procedure rather than perform a difficult, time-consuming search for what is almost certainly a normal parathyroid. Before terminating an exploration of a patient suspected of having multiple hyperfunctioning parathyroid glands, the decrease of IOPTH should be well into the normal range, usually to less than 20 pg/ml, not simply more than 50 % of the baseline value.

This is especially true in reoperations on patients with recurrent or persistent hyperparathyroidism or in patients undergoing parathyroid exploration after previous thyroidectomy. Even when one has access to the previous operative and pathology reports, it is frequently difficult to be certain how many parathyroids were removed or damaged and how many remain in the neck. If during such a re-exploration an enlarged parathyroid is removed and IOPTH drops appropriately, further exploration to identify the remaining parathyroids, which may not even be present, can be avoided.

Carneiro-Pla has suggested the use of office-based ultrasound-guided bilateral jugular venous sampling to help localize parathyroid adenomas. This technique can also be used intraoperatively when a parathyroid adenoma cannot be found after thorough exploration. Blood samples are drawn directly from each jugular vein and IOPTH measured on each sample. A marked differential between the IOPTH in the two veins would prompt further exploration on the side with the higher value. This technique has proven useful in finding parathyroid adenomas cephalad to their usual locations.

IOPTH can also be used in conjunction with intraoperative FNA of thyroid nodules or other neck masses. If an intrathyroidal parathyroid is suspected during exploration, rather than perform a thyroid lobectomy, an intraoperative FNA can be performed and the needle rinsed with a small volume of saline which is sent for IOPTH. High PTH levels confirm the suspicion of a parathyroid gland. The same technique can be used to assess other neck masses rather than waiting for frozen section pathology.

Conclusion

IOPTH is an invaluable aid to the parathyroid surgeon. Access to this test permits the performance of MIP with a high likelihood of cure. Performance of MIP without IOPTH may result in a higher failure rate and should be discouraged. IOPTH is also valuable in difficult bilateral explorations and in reoperative surgery.

Recommended Reading

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