Disparity between Preoperative and Pre-Excisional Intraoperative Parathyroid Hormone in Parathyroid Surgery

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Int Arch Otorhinolaryngol 2018;22:382–386.

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Abstract

Introduction Intraoperative parathyroid hormone (ioPTH) testing is a widely accepted standard for assessing the parathyroid gland function. A decline of preoperative parathyroid hormone (PTH) levels by more than 50% is one accepted measure of parathyroid surgery adequacy. However, there may be a variation between preoperative PTH levels obtained at a clinic visit and pre-excisional ioPTH.

Objective Our study explores the differences between preoperative PTH and pre-excisional ioPTH levels, and the potential impact this difference has on determining the adequacy of parathyroid surgery.

Methods A retrospective study that consisted of 33 patients that had undergone parathyroid resection between September 2009 and March 2016 at a tertiary academic center was performed. Each subject's preoperative PTH levels were obtained from clinic visits and pre-excisional ioPTH levels were recorded along with the time interval between the measurements.

Results There was a significant difference between the mean preoperative PTH and the pre-excisional ioPTH levels of 147 pg/mL (95% confidence interval [CI] 11.43 to 284.47; $p = 0.0396$). The exclusion of four outliers revealed a further significant difference with a mean of 35.09 pg/mL (95% CI 20.27 to 49.92; $p < 0.0001$). The average time interval between blood draws was 48 days + 32 days. A weak correlation between the change in PTH values and the time interval between preoperative and pre-excision blood draws was noted ($r2 = 0.15$).

Conclusion Our study reveals a significant difference between the preoperative PTH levels obtained at clinic visits and the pre-excisional intraoperative PTH levels. We recommend routine pre-excisional intraoperative PTH levels, despite evidence of elevated preoperative PTH levels, in order to more accurately assess the adequacy of surgical resection.

Keywords
- parathyroidectomy
- parathyroid hormone
- parathyroid neoplasms

Introduction

Hyperparathyroidism is an endocrine disorder characterized by excessive parathyroid hormone (PTH) and a common cause of hypercalcemia. The PTH is a major component of calcium metabolism and it is produced by the parathyroid glands. Disorders of the parathyroid glands generally involve excessive secretion of PTH leading to a variety of systemic symptoms. In the cases of primary hyperparathyroidism, 87–91% are caused by a single adenoma of the parathyroid gland.[1] Other causes, although less common, may include double adenomas, four-gland disease, and parathyroid carcinoma.[1] It presents more

received November 17, 2017
accepted February 19, 2018
published online March 29, 2018

DOI https://doi.org/10.1055/s-0038-1635574.
ISSN 1809-9777.

commonly in women and those over the age of 50.[2] Classical symptoms of hyperparathyroidism include kidney stones, abdominal pain, neurocognitive symptoms, bones pain, muscle weakness, and fatigue. Other symptoms may exist and vary symptomatically between individual, and individuals may even be asymptomatic.

Surgical intervention is the only definite treatment for the disorder. Although medical management may be attempted for the treatment of hyperparathyroidism, greater treatment and patient outcomes generally favor a surgical approach rather than medical management.[3] The main aim of the surgical treatment is to reduce the levels of PTH that lead to hypercalcemia and establish a normocalcemic level in the individual. The previously traditional approach consisted of a bilateral central compartment parathyroid gland exploration and subsequent excision of the diseased glands. Minimally invasive parathyroidectomy has now become the more common surgical technique due to advancements in imaging technology, surgical instrumentation, technique, and the use of intraoperative parathyroid hormone (ioPTH) monitoring to rapidly determine the adequacy of the surgical excision of the glands.[4] When compared with the more invasive use of the bilateral neck exploration and surgical resection, the minimally invasive techniques lead to lower rates of complications (lower rates of postoperative hypocalcemia and recurrent laryngeal nerve injury), shorter hospital stays, with an efficacy equal to that of the bilateral neck exploration method.[5]

Due to the relatively short half-life of the PTH, PTH measurements serve as a useful laboratory measurement for surgical adequacy. Preoperative PTH levels are routinely measured to confirm disease state and severity, such as during a clinic visit. A drop in the ioPTH level by more than 50% of the preoperative PTH level at the 10–15-minute mark post-excision is considered a standard of care accepted measure of surgery adequacy, and the vast majority of these patients are cured. However, even this test has false-positive and false-negative results. At times, the reduction in PTH level hovers around 50%, leading to further surgical exploration, which may or may not be necessary. There have been case reports of delayed double adenoma recognition leading to second surgeries, placing the patient at a high perioperative risk for complications. Therefore, there is a monumental importance placed on the PTH value measured before the surgery, as it is used for comparative analysis to the ioPTH post-excision.

At our institution, it is the senior surgeon's (T.H.) practice to obtain a pre-excisional ioPTH regardless of a documented preoperative level in the records from regular clinic visits. Surgical excision of the gland occurs after this blood measurement is taken in the operative room. Discrepancies between the preoperative PTH and pre-excisional ioPTH have been noted. Due to the potential impact of quantifying adequacy of surgery, we sought to explore the differences in these levels.

The study aims to analyze the disparity between preoperative PTH and pre-excisional ioPTH in patients who have undergone surgical correction of their hyperparathyroidism. We hypothesize that if a consistent disparity is noted, then routine pre-excisional ioPTH should be considered a standard practice when using PTH levels to assess surgical adequacy, particularly in cases of non-localizing adenomas or possible double adenomas.

Methods

After receiving exemption by the Institutional Review Board at our institution, we conducted a retrospective chart review and analysis of adult patients treated for hyperparathyroidism at a tertiary academic care center from September 2009 to March 2016.

Each patient had a full medical workup for hyperparathyroidism to confirm the diagnosis.

Various variables including elevated preoperative PTH, symptomatic presentations, medical therapy, bone scans, and progression of the disease were taken into account before surgical consideration. The patients included in the study consisted of those who had preoperative PTH levels determined at clinic visits and pre-excisional ioPTH measured and who subsequently underwent parathyroid surgery for the correction of their hyperparathyroidism. The patients not included in the study are those that did not have available data regarding preoperative or pre-excisional laboratory values or whose data from the blood draw could not be confirmed.

The patients in the study had hyperparathyroidism either from hyperplasia or adenomas. The minimally invasive surgical approach was utilized for parathyroid resection. Each patient had a known recorded preoperative PTH level taken during or prior to outpatient clinical visits. In these clinic visits, blood samples were taken and stored in serum separating tubes (SSTs). These tubes were then sent for PTH and calcium level analysis with the use of the VITROS 5600 Integrated System (Ortho Clinical Diagnostics, Raritan, NJ, USA).

The surgical team performed pre-excisional ioPTH levels following anesthesia induction. The blood was drawn from the patient and stored in ethylenediaminetetraacetic acid (EDTA) tubes and transferred for analysis. In addition, the post-excisional PTH levels were measured in each patient to determine the drop in PTH level from previously measured elevated PTH values before initiation of surgical resection.

The study evaluated the patients' demographics, etiology of hyperparathyroidism, date and level of the preoperative PTH from clinic visits, and the date and level of the pre-excisional ioPTH. The disparity between preoperative the PTH and pre-excisional ioPTH values was calculated along with *t*-test comparisons and statistical significance ($p < 0.05$).

Results

Patient and Disease Characteristics

A total of 33 patients met the criteria for inclusion in the study. There was a female predominance noted with 22 females and 11 males. The average age at the time of surgery for the female patients was 59.1 and the average age for the male patients was 46.3. The primary diagnosis found within the patient population is summarized in ►**Table 1**. The primary diagnosis was parathyroid adenoma (72.7%) followed by four-gland hyperplasia (27.3%). Of the 24 patients with parathyroid adenoma, 21 had unilateral adenomas, while 3 had double adenomas. In addition,

Table 1 Disease characteristic prevalence among the patient population

Disease Type	*Total*
Parathyroid adenoma	24
Four-gland hyperplasia (primary hyperparathyroidism or renal hyperplasia)	9
Primary hyperparathyroidism	*3*
Renal hyperplasia	*6*
Overall Total	33

the four-gland hyperplasia group consisted of renal hyperplasia and primary hyperparathyroidism.

Preoperative PTH and Pre-Excisional Intraoperative PTH Analysis

Each patient had a preoperative PTH, measured at the clinic, and a pre-excisional ioPTH, measured before the surgical incision was initiated, and the difference between these two values was calculated for each patient, with a total of 33 patients. ►**Table 2** summarizes the data pertaining to PTH difference measurements. Four patients, three with renal parathyroid hyperplasia and one with a parathyroid adenoma, who were outliers and had a difference of over 400 pg/mL between their preoperative PTH and ioPTH, were excluded from several calculations as shown in the tables. Calculations that both included and excluded these patients are in ►**Table 2**. The average PTH difference in all patients (147.00 pg/mL) and all the patients excluding the outliers (35.09 pg/mL) was calculated. Statistically significant differences were noted both when including all patients ($p = 0.0347$) and all the patients with exclusion of the outliers ($p < 0.0001$).

Parathyroid Adenoma PTH vs Four-gland Hyperplasia PTH

A total of 24 patients were diagnosed with parathyroid adenoma. Statistical analyses regarding parathyroid adenoma are summarized in ►**Table 3**. One patient had a difference between their preoperative and pre-excisional intraoperative PTH value of 864 pg/mL and was excluded due to have a difference greater than 400 pg/mL. After exclusion of this one patient, an average PTH difference of 21.98 pg/mL was noted along with statistical significance ($p = 0.0396$).

A total of nine patients were diagnosed with four-gland hyperplasia in which six were due to renal hyperplasia and three due to primary hyperparathyroidism. Three patients with renal hyperplasia had a preoperative and intraoperative PTH difference of over 400 pg/mL. The statistical analysis of these pathologies was calculated, and both included and excluded those with PTH differences greater than 400 pg/mL (►**Table 3**). When excluding the three renal hyperplasia patients, an average PTH difference of 74.66 pg/mL was calculated along with significance ($p = 0.0121$). No statistical significance was found when examining all patients with four-gland hyperplasia or when stratifying the four-gland hyperplasia (renal hyperplasia and primary hyperparathyroidism) group with or without the excluded patients.

Length of Time Intervals between PTH Measurements Analysis

The lengths of time between the dates of preoperative PTH and pre-excisional ioPTH were calculated for each patient. The average length of time between these dates was calculated to be 48 days ± 32 days. The linear regression analyzing the relationship between length of time between PTH measurements and the PTH differences in the patients revealed an extremely weak correlation of $r^2 = .15$.

Table 2 Statistical data for PTH level difference among the patient population

Preoperative PTH and pre-excisional intraoperative PTH mean difference (pg/mL)		95% CI (pg/mL)	*p*-value
All patients	147.00	[11.43; 284.47]	***0.0347***
All patients, except those with PTH differences greater than 400 pg/mL	35.09	[20.27; 49.92]	< ***0.0001***

Abbreviations: CI, confidence interval; PTH, parathyroid hormone.

Table 3 Stratification of statistical data for parathyroid hormone (PTH) levels based on pathology

Preoperative PTH and pre-excisional intraoperative PTH mean difference (pg/mL)		95% CI (pg/mL)	*p*-value
Parathyroid adenoma	57.05	[−12.21; 126.34]	*0.1906*
Parathyroid adenoma except those with PTH differences greater than 400 pg/mL	21.98	[12.38; 31.58]	***0.0396***
Four-gland hyperplasia	345.55	[−33.35; 724.45]	*0.1116*
Four-gland hyperplasia, except those with PTH differences greater than 400 pg/mL	74.66	[35.66; 113.66]	***0.0121***
Primary hyperparathyroidism	65.00	[52.00; 78.00]	*0.1272*
Renal hyperplasia	485.33	[−60.98; 1032.36]	*0.1419*
Renal hyperplasia, except those with PTH differences greater than 400 pg/mL	84.33	[25.93; 142.73]	*0.1295*

Abbreviation: CI, confidence interval.

Table 4 Parathyroid hormone (PTH) values used to determine the necessity of re-exploration

PTH value used to determine need for re-exploration	Need for re-exploration	Borderline for re-exploration
Preoperative PTH	2/33 (6.1%)	4/33 (12.1%)
Intraoperative PTH	0/33 (0%)	0/33 (0%)

Preoperative PTH, Post-surgical PTH, and Consideration for Re-Exploration

The 50% reduction rule was assessed for the potential need for re-exploration. No patients underwent re-exploration in the study however, we determined how the preoperative PTH and pre-excisional intraoperative PTH may have influenced the need for re-exploration (►**Table 4**). If using the preoperative PTH values alone, 6.1% met the criteria for re-exploration, while 12.1% were borderline for re-exploration. None of the patients met the criteria when using the pre-excisional intraoperative PTH values.

Patient Follow-up

All patients were closely followed postoperatively in regularly scheduled clinic visits over time. PTH and calcium levels were measured in all the patients during each of these scheduled visits. There was no evidence of hypercalcemia or recurrent hyperparathyroidism in any patient to date.

Discussion

The advancements in laboratory monitoring of PTH levels have allowed surgeons to more accurately assess the success of surgical resection of the parathyroid glands. This innovation in surgery has become the standard of parathyroid surgery and has reduced the need of other techniques, such as frozen section analysis and four-gland exploration.[6] Intraoperative PTH monitoring has shown to be both a superior approach to determine the adequacy of gland section, be more cost effective, and reduce the need for more invasive approaches to surgery.[6] Using these advantages, the use of minimally invasive techniques is becoming the standard of care. A decline in the PTH to the normal range, and/or a greater than 50% delta drop in the level, is considered to be the standard for ensuring adequacy of surgical resection. Therefore, the accuracy of the pre-excisional ioPTH value is critical to the accuracy of the delta value used for determining completion of surgery.

Every test has a potential for false-positive and false-negative results. Intraoperative parathyroid hormone monitoring is no different in this respect, particularly when the decision of whether or not to perform further surgery rests on the percentage decline of this level. The test results are highly dependent on the parameters used. If the delta decline is not "sufficient," the patient will likely undergo further blood draw and exploration, which increases the operative risk, time, and cost. When further disease is discovered, the increased interventions are justified, but in cases in which further exploration is negative for the disease, the benefit to cost/risk ratio is less favorable. Our study demonstrates a statistically significant difference of at least 35 pg/mL between the preoperative and pre-excisional ioPTH values. Therefore, pre-excisional ioPTH levels are critical to reduce the potential for false-positive and false-negative delta PTH drops intraoperatively. Accuracy of the pre-excisional levels is one way of minimizing false-positive and false-negative results.

It is unclear why this disparity between intraoperative and preoperative PTH values exists. The specimen processing of routine outpatient laboratory draws and intraoperative levels is different not only with respects to the speed of results, but also to the technique. There currently is not a standard method of PTH processing and analysis in the laboratory setting. Institutional variations exist which have hindered the creation of specific guidelines. This is critical as laboratory measurements of PTH are the mainstay of determining the adequacy of parathyroid surgery. Most centers use second or third generation immunoassay methods for PTH analysis.[7] Both second and third generation immunoassay methods consist of using two monoclonal antibodies directed against different regions of the N-terminal and C-terminal residue to measure PTH levels.[7] Various intraoperative systems reportedly produce results at 5, 8 and 20 minutes, for example.

One consideration is the storage of the sample; storage in whole blood or in serum with ethylenediaminetetraacetic acid (EDTA) showed more stability than those without anticoagulants.[7] Location of the blood draw for PTH also plays a role, and PTH values were higher when blood was taken from the central venous system, such as the internal jugular vein, as compared with peripheral sources of blood.[7] Regardless, while similar, the various assays do not process specimens identically, and therefore the results are not directly comparable. Thus, there is likely an inherent quantitative difference uniformly between the methods used. To obtain the most consistent and reliable information, practitioners should plan to run preexcision and post-excision PTH samples on the same assay, on blood drawn from the same site.

Minimally invasive parathyroidectomy has become the standard method of surgical resection due to parathyroid pathology. It has shown to be cost effective and successful in terms of curative rates. Removal of the parathyroid glands with autoimplantation of one or few glands is one method commonly used to reduce the level of high PTH, but also to avoid the possibility of hypoparathyroidism.[8] In other cases, complete removal of the parathyroid glands may be necessary. Failure of achieving an appropriate drop in PTH would warrant a surgical gland exploration. As mentioned, the value of PTH measured becomes critical when deciding whether a gland exploration is necessary. Establishment of accurate PTH measurements would facilitate in decision making of whether a gland exploration is necessary. Gland exploration requires increased operating room time for the patient, along with higher costs. Due to the invasive nature of a gland exploration, there is higher potential for surgical complications, including recurrent and superior laryngeal nerve palsy, iatrogenic thyroid injury, and unintentional hypoparathyroidism. In skilled hands, these complications are rare.

However, a more serious issue is when the false-positive result (perceived PTH reduction $> 50\%$ that is not accurate) convinces a practitioner to conclude surgery prematurely. In one study that was a retrospective review of 723 patients, it was reported that 5 of 21 operative failures were secondary to false-positive ioPTH levels.[9] While uncommon, in these cases, patients are not recognized to have persistent hyperparathyroidism until they undergo outpatient blood work. Given the statistically significant difference between preoperative PTH and pre-excisional ioPTH levels we found in our small patient population, it is reasonable to assume such variations may have been responsible for the false-positive results in the above-mentioned study.

Furthermore, patients with persistent disease incur more cost and have greater surgical risks. They typically undergo further diagnostic imaging and blood test, and then ultimately revision exploration in a previously operated field, which may have varying degrees of scar tissue and anatomic distortion from prior dissection, lengthening surgical time and therefore further compounding the cost. In addition, there are the psychosocial costs, including the additional time off work for the patients and their transporters for further surgery, potential for hospital admission, the patient's mental preparation to accept additional higher risk surgery, as well as trust issues with the practitioner with respects to chances for surgical success.

With respects to patient morbidity, the risks for nerve injury, hemorrhage, and hypoparathyroidism are significantly increased, as are the operative times and potential for hospital admission with repeated surgery.[5] The surgical planes may be significantly distorted from prior surgery, complicating nerve identification despite the use of intraoperative monitors. Dissections are typically more laborious and lengthy and therefore require more anesthetic and potential need for hospital stay for what is otherwise typically an outpatient surgery. Accurate intraoperative testing at the first surgery may prevent this scenario.

The most common potential complication of surgery is recurrent laryngeal nerve injury. Unilateral injury can result in hoarseness and difficulty swallowing. Bilateral nerve is a feared, yet rare, complication that can result in airway obstruction leading to an emergency need for airway management. Intraoperative nerve monitoring allows continuous monitoring of the nerve, provided that the probe is placed appropriately, and the machine is functioning. No consensus on its use has been established, and debate still exists whether nerve monitoring reduces the occurrence of nerve injury in patients undergoing revision surgery.[10,11] However, avoidance of revision surgery provides the best opportunity to reduce the risk of recurrent laryngeal nerve injury.

Our study is limited by a small sample size. However, despite the small sample size, the delta between preoperative and pre-excisional ioPTH was statistically significant and independent of the length of time between blood draws. A larger patient series could be conducted to further confirm the results and potentially evaluate the disparity in PTH measurements between the various assays/systems available.

Conclusion

We have demonstrated statistically significant differences between the preoperative PTH and pre-excisional ioPTH levels. The exact reasons behind the disparity are equivocal and based on a variety of factors, such as type of immunoassay, machine type used, storage of PTH, timing, blood source, and possible other reasons may also exist. Accuracy of the PTH levels is essential to assess whether surgical resection was successful, and if further surgical exploration is warranted. In a majority of cases, fortunately this disparity did not impact on the patients' outcome. However, we did identify cases in which the variance in the preoperative levels could have negatively impacted a patient's outcome and surgical decisions. Due to the clinical significance of accurate PTH, establishing a standard and accurate method of PTH measurements would facilitate the efficacy of parathyroid surgery. We therefore recommend drawing a pre-excisional ioPTH baseline level despite the documentation of preoperative PTH elevation in the laboratory records. In addition, accuracy is further improved if the pre-excisional and post-excisional levels are drawn from the same site.

References

1 Farrag T, Weinberger P, Seybt M, Terris DJ. Point-of-care rapid intraoperative parathyroid hormone assay of needle aspirates from parathyroid tissue: a substitute for frozen sections. Am J Otolaryngol 2011;32(06):574–577
2 Calò PG, Pisano G, Loi G, et al. Intraoperative parathyroid hormone assay during focused parathyroidectomy: the importance of 20 minutes measurement. BMC Surg 2013;13(01):36
3 Conzo G, Perna AF, Napolitano S, et al. Partial response to cinacalcet treatment in a patient with secondary hyperparathyroidism undergoing hemodialysis: a case report. J Med Case Reports 2012;6(01):417. Doi: 10.1186/1752-1947-6-417
4 Sohn JA, Oltmann SC, Schneider DF, Sippel RS, Chen H, Elfenbein DM. Is intraoperative parathyroid hormone testing in patients with renal insufficiency undergoing parathyroidectomy for primary hyperparathyroidism accurate? Am J Surg 2015;209(03):483–487
5 Chen H, Pruhs Z, Starling JR, Mack E. Intraoperative parathyroid hormone testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. Surgery 2005;138(04):583–587, discussion 587–590
6 Gapany M. Are Frozen Sections Useful and Cost-effective in the Era of Intraoperative qPTH Assays? Yearbook Otolaryngol Head Neck Surg 2006;20(06):213–214
7 Hanon EA, Sturgeon CM, Lamb EJ. Sampling and storage conditions influencing the measurement of parathyroid hormone in blood samples: a systematic review. Clin Chem Lab Med 2013;51 (10):1925–1941
8 Conzo G, Della Pietra C, Tartaglia E, et al. Long-term function of parathyroid subcutaneous autoimplantation after presumed total parathyroidectomy in the treatment of secondary hyperparathyroidism. A clinical retrospective study. Int J Surg 2014;12(Suppl 1): S165–S169. Doi: 10.1016/j.ijsu.2014.05.019
9 Lew JI, Rivera M, Irvin GL III, Solorzano CC. Operative failure in the era of focused parathyroidectomy: a contemporary series of 845 patients. Arch Surg 2010;145(07):628–633
10 Al-Qurayshi Z, Randolph GW, Alshehri M, Kandil E. Analysis of Variations in the Use of Intraoperative Nerve Monitoring in Thyroid Surgery. JAMA Otolaryngol Head Neck Surg 2016;142(06):584–589
11 Hei H, Zhou B, Qin J, Song Y. Intermittent intraoperative nerve monitoring in thyroid reoperations: Preliminary results of a randomized, single-surgeon study. Head Neck 2016;38(Suppl 1): E1993–E1997