Intraoperative parathormone monitoring to predict operative success in patients with normohormonal hyperparathyroidism

Heather Stuart, MD, MSc
Basem Azab, MD
Omar Picado Roque, MD, MSCTI
Janice Pasieka, MD
John I. Lew, MD

Accepted July 20, 2021

Presented in part at the 38th Annual Meeting of the American Association of Endocrine Surgeons, Apr. 2–4, 2017, Orlando, Fla.

Correspondence to:
H. Stuart
Room 5199, 2775 Laurel St
Vancouver BC V5Z 1M9
heather.stuart@vch.ca

Cite as: Can J Surg 2022 July 28; 65(4). doi: 10.1503/cjs.013220

Background: It is unclear whether parathyroidectomy guided by intraoperative parathormone (PTH) monitoring is predictive of operative success in patients with normohormonal hyperparathyroidism (nhHPT), a variant of primary hyperparathyroidism (pHPT) in which patients develop clinical manifestations similar to those of pHPT. This study examined intraoperative PTH monitoring in patients undergoing parathyroidectomy for nhHPT.

Methods: We performed a retrospective review of prospectively collected data from adult (age > 18 yr) patients who underwent parathyroidectomy for pHPT at 1 of 2 North American medical centres (in Calgary, Alberta, Canada, or Miami, Florida, United States) between 2007 and 2015. In patients with nhHPT, we used the criterion of an intraoperative decrease of more than 50% in PTH after abnormal gland excision. We defined operative success as continuous eucalcemia more than 6 months after parathyroidectomy.

Results: Of 333 patients, 38 (11.4%) had nhHPT, with mean preoperative calcium and PTH levels of 2.7 mmol/L and 53 pg/dL, respectively. An intraoperative decrease of more than 50% in PTH level was seen in 27 patients (71.0%) with nhHPT and 265 patients (89.8%) with classic pHPT at 5 minutes (p < 0.001); the corresponding values at 20 minutes were 35 (92.1%) and 286 (96.9%). Although 5 patients (13.2%) with nhHPT did not reach this criterion until 20 minutes, the rate of operative success was still 97.0% at long-term follow-up (mean 13 mo, range 6–67 mo). Of the 38 patients, 3 (7.9%) did not have an intraoperative decrease of more than 50% in PTH level by 20 minutes. Two of the 3 achieved operative success and remained normocalcemic, and 1 developed recurrent disease at 12 months.

Conclusion: Parathyroidectomy guided by intraoperative PTH monitoring accurately predicted operative success in patients with nhHPT. Intraoperative PTH monitoring may also help identify multiglandular disease in patients with nhHPT, using criteria similar to those in classic pHPT, with comparable operative success.
Primary hyperparathyroidism (pHPT) affects about 50 per 100,000 people annually, and its clinical manifestations have adverse effects on bone, kidney, and cognitive function. With the advent of improved and more widespread methods of biochemical detection, neck imaging, and bone evaluation and screening, the incidence of pHPT continues to increase. The diagnosis of classic pHPT is confirmed biochemically by hypercalcemia in the setting of elevated serum parathyroid hormone (PTH) levels. Over time, the biochemical presentation of this disease has evolved, with a subset of patients presenting more frequently with biochemically mild variants of pHPT (normocalcemic hyperparathyroidism [ncHPT] or normohormonal hyperparathyroidism [nHPT]).

Since the 1990s, there has been an increasing incidence of nHPT as a result of a greater appreciation for subtle PTH imbalances. The rate of nHPT ranges between 5% and 21%, likely owing, in part, to variation in the upper limit of normal serum PTH level over time and between different PTH assays. Despite the biochemical profile of nHPT, affected patients have clinical manifestations of hypercalcemia similar to those of patients with classic pHPT (i.e., nephrolithiasis, bone disease, cognitive symptoms). Although the underlying cause of nHPT remains unclear, it may represent an early form of pHPT, a lower PTH set point or a technical inability to detect circulating forms of PTH with current assays. With increased routine biochemical testing, neck imaging studies and measurements for bone mineral evaluation, patients with nHPT currently undergo surgical treatment because of preoperative symptoms and the finding of hyperfunctioning gland(s) at parathyroidectomy. It is recognized that nHPT is a challenge to interpret and that it is a condition of abnormal parathyroid gland function in the setting of hypercalcemia.

Some authors have described ncHPT as a forme fruste of classic pHPT in which patients develop the clinical manifestations of pHPT over time. Patients with nHPT who have inappropriately nonsuppressed PTH levels that lie within normal range in the setting of elevated or high-normal serum calcium levels also present with symptoms similar to those seen in patients with classic pHPT and experience similar postoperative resolution of disease-related disorders. Nevertheless, it remains controversial whether patients with nHPT should undergo parathyroidectomy because the natural history of nHPT remains poorly defined and the benefits of surgical management questioned. Although not discussed in recent guidelines, patients with nHPT often undergo surgical exploration if they meet the same symptomatic or asymptomatic criteria as patients with classic pHPT.

Many surgeons use PTH monitoring during parathyroidectomy to guide and confirm removal of all hyperfunctioning parathyroid glands. An intraoperative decrease in PTH level of more than 50% at 10 minutes, or the “Miami criterion,” is often used to guide parathyroidectomy, and this protocol has been found to be at least 98% accurate in predicting operative success in patients with classic pHPT at 6 months. Given the differing biochemical profiles of patients with pHPT, determining operative success based on the Miami criterion is of interest in patients with nHPT who have normal PTH levels preoperatively.

This study evaluated the utility of intraoperative PTH monitoring and whether a decrease in PTH level of more than 50% during parathyroidectomy can be used to predict operative success in patients with nHPT. We hypothesized that the intraoperative PTH level can be used to accurately predict operative success in patients with nHPT and that the criterion of achieving an intraoperative decrease of more than 50% in PTH level may be applied to this population.

**Methods**

We conducted a retrospective cohort study using databases from 2 tertiary medical centres in Calgary, Alberta, Canada, and Miami, Florida, United States, between 2007 and 2015. Approval was granted by the University of Miami research ethics board and the University of Calgary Conjoint Health Research Ethics Board. All patients underwent parathyroidectomy guided by intraoperative PTH monitoring.

---

atteint ce critère avant 20 minutes, le taux de succès opératoire était encore de 97,0 % lors du suivi à long terme (moyenne 13 mois, intervalle 6–67 mois). Sur les 38 patients, 3 (7,9 %) n’ont pas eu de diminution peropératoire de plus de 50 % du taux de PTH avant 20 minutes. Pour 2 de ces 3 patients, l’opération a réussi; ils sont demeurés normocalcémiques. L’autre patient a développé une maladie récurrente à 12 mois.

**Conclusion :** La parathyroïdectomie guidée par la surveillance peropératoire de la PTH a permis de prédire avec précision le succès opératoire chez les patients atteints de nHPT. La surveillance peropératoire de la PTH peut également aider à détecter une maladie multiglandulaire chez les patients atteints de nHPT, par l’utilisation de critères similaires à ceux de la pHPT classique, avec succès opéra­toire comparable.
Study patients were older than 18 years and had a diagnosis of pHPT based on preoperative serum calcium and PTH levels. Patients with classic pHPT were defined by preoperative PTH levels greater than 65 pg/dL and hypercalcemia. Patients with preoperative PTH levels of 65 pg/dL or less, with elevated or near-normal calcium levels, were considered to have nhHPT. The last outpatient PTH level measured before surgery was used to categorize patients.

Data reviewed included patient demographic characteristics, intraoperative PTH dynamics, and pre- and postoperative serum calcium and PTH levels. All patients underwent parathyroid localization studies via sestamibi (MIBI) scans or ultrasonography, or both, preoperatively. Data regarding other imaging modalities and correlation with intraoperative findings were not collected. All patients were followed for a minimum of 6 months after parathyroidectomy. Patients with secondary, tertiary or familial hyperparathyroidism, multiple endocrine neoplasia syndromes, renal insufficiency, parathyroid carcinoma, concurrent thyroid surgery or redo parathyroid surgery were excluded from the study.

Patient selection for parathyroidectomy was determined in accordance with previously published guidelines for the operative indications for pHPT. Patients underwent focused parathyroidectomy or bilateral neck exploration based on preoperative imaging and surgeon preference.

The criterion used to predict successful parathyroidectomy was an intraoperative decrease of more than 50% in PTH level from the highest preincision or pre-excision level 10 minutes after excision of all abnormal parathyroid tissue. If there was an insufficient decrease in PTH level at 10 minutes, the operation was converted to bilateral neck exploration or the PTH level was measured at 20 minutes, at the surgeon’s discretion. Patients who did not show a decrease of more than 50% in PTH level by 20 minutes underwent bilateral neck exploration.

In patients in whom bilateral neck exploration was performed, additional abnormal-appearing glands were removed, followed by intraoperative PTH measurement. In Miami, multiglandular disease was defined as persistently elevated intraoperative PTH levels despite removal of 1 hypersecreting gland at the time of initial operation or when removal of a single gland resulted in operative failure. In Calgary, multiglandular disease was defined as more than 1 histologically enlarged hypercellular gland identified intraoperatively or when removal of a single gland resulted in operative failure.

We defined operative success as eucalcaemia more than 6 months after parathyroidectomy, and operative failure as hypercalcaemia greater than the reference range more than 6 months after parathyroidectomy. We defined recurrent disease as hypercalcaemia and PTH levels above the normal reference range more than 6 months after successful parathyroidectomy.

Statistical analysis

We used the Student t test and the χ² test to perform statistical analysis. A p value < 0.05 was considered statistically significant.

Results

Of 333 patients identified from the joint databases, 295 (88.6%) had classic pHPT, and 38 (11.4%) had nhHPT (Table 1). There were no differences in age or sex between the 2 groups. Preoperative calcium values (2.7 mmol/L v. 2.8 mmol/L) and PTH values (53 pg/dL v. 145 pg/dL) were significantly lower in the nhHPT group than in the classic pHPT group (p < 0.001 for both) (Table 2). All patients underwent preoperative imaging, 296 (88.9%) with ultrasonography, 259 (77.8%) with sestamibi scintigraphy, and 233 (70.0%) with both modalities.

Mean peak preincision/pre-excision intraoperative PTH values were significantly higher in patients with classic pHPT than in those with nhHPT (263 pg/dL v. 133 pg/dL, p < 0.05). Twenty-seven patients (71.0%) in the nhHPT group and 265 patients (89.8%) in the classic

| Table 1. Mean preoperative calcium and parathormone levels in patients with normohormonal hyperparathyroidism and primary hyperparathyroidism at the 2 study centres |
| --- |
| Group; variable | Centre; no. (%) of patients* |
| Calgary | Miami | n = 62 | n = 271 |
| **Classic pHPT** (n = 295) | | |
| Preoperative calcium level, mean ± SD, mmol/L | 2.8 ± 0.2 | 2.8 ± 0.2 |
| Preoperative PTH level, mean ± SD, pg/dL | 113 ± 50 | 151 ± 60 |
| **nhHPT** (n = 38) | | |
| Preoperative calcium level, mean ± SD, mmol/L | 2.6 ± 0.1 | 2.7 ± 0.1 |
| Preoperative PTH level, mean ± SD, pg/dL | 52 ± 10 | 54 ± 9 |

nhHPT = normohormonal hyperparathyroidism; pHPT = primary hyperparathyroidism; PTH = parathormone; SD = standard deviation.

*Except where noted otherwise.

| Table 2. Patient demographic characteristics | No. (%) of patients* |
| --- | --- |
| **Classic pHPT** n = 295 | nhHPT n = 38 | p value |
| Age, mean ± SD, yr | 59 ± 14 | 58 ± 10 | 0.5 |
| Female sex | 239 (81.0) | 28 (73.7) | 0.3 |
| Preoperative calcium level, mean ± SD, mmol/L | 2.8 ± 0.2 | 2.7 ± 0.1 | < 0.001 |
| Preoperative PTH level, mean ± SD, pg/dL | 145 ± 61 | 53 ± 9 | < 0.001 |
| Preoperative eucalcaemia | 7 (2.4) | 2 (5.3) | 0.3 |

nhHPT = normohormonal hyperparathyroidism; pHPT = primary hyperparathyroidism; PTH = parathormone; SD = standard deviation.

*Except where noted otherwise.
The number of glands removed or incidence of multiglandular disease between the nhHPT and classic pHPT groups.

The rate of operative success was 99.0% (292/295) among patients with classic pHPT and 97.4% (37/38) among those with nhHPT.

**Discussion**

We observed a rate of nhHPT of 11%. This value is consistent with published rates of 0.3%–22.5%. In our nhHPT group, an intraoperative decrease of more than 50% in PTH level by 10 or 20 minutes accurately predicted operative success at a mean follow-up duration of 13.6 months. At 10 minutes, 84% of patients with nhHPT achieved this criterion, compared to 94% of those with classic pHPT. The corresponding values at 20 minutes were 92% and 97%. These trends in intraoperative PTH dynamics suggest a slower rate of PTH decrease in patients with nhHPT than in those with classic pHPT. This is similar to the results of Alhefdhi and colleagues, who found that 4.9% of patients with mild hyperparathyroidism did not achieve an intraoperative decrease of more than 50% in PTH level until 20 minutes. Trinh and colleagues compared rates of decrease in intraoperative PTH level between patients with classic pHPT and those with nhHPT, and found a direct association between baseline PTH level and rate of intraoperative PTH degradation. Although the physiologic basis for this more gradual decline of intraoperative PTH level in patients with nhHPT remains unclear, a possible explanation is that, in patients with lower preoperative PTH levels, there may be less suppression of normally functioning parathyroid glands, leading to a slower relative decrease in PTH level intraoperatively.

In the present study, all patients with nhHPT who did not have an intraoperative decrease of more than 50% in PTH level at 10 minutes but achieved this decrease by 20 minutes had operative success at 6 months. Graves and colleagues examined intraoperative PTH kinetics in patients with mild hyperparathyroidism and found that there was a trend toward a longer time to achieve an intraoperative decrease of more than 50% in PTH level in those with nhHPT than in those with classic pHPT. Among patients with nhHPT who did not have an intraoperative decrease of more than 50% in PTH level by 10 minutes, the median time to reach this criterion was 25 minutes. Khan and colleagues reported that PTH measurement at 20 minutes significantly reduced the need for bilateral neck exploration in patients with classic pHPT by enabling more patients to reach an intraoperative decrease of more than 50% in PTH level. Based on these findings, it is reasonable to extrapolate that measuring the PTH level at 20 minutes during parathyroidectomy may optimize operative success in patients with nhHPT.
The rate of in the nhHPT group in our study, 8%, is lower than values reported in the literature (12%–59%). In 1 report, a rate of multiglandular disease of 29% was found in patients with nhHPT, higher than that seen in classic pHPT. In another study, multivariate analysis did not show any statistically significant association of multiglandular disease with any pHPT variant (classic pHPT 16.5% v. ncHPT 21.7% v. nhHPT 9.1%). The observed variability in multiglandular disease rates in these studies is likely multifactorial and includes factors such as population; sample size; varied definitions of multiglandular disease based on quantitative assessment (i.e., intraoperative PTH level) versus qualitative assessment (i.e., size, colour, histologic features); surgeon experience, judgment and preference; and initial surgical approach used.

The rate of bilateral neck exploration among our patients with nhHPT was higher than that for patients with classic pHPT (32% v. 19%). Similar findings were reported in other surgical series showing a rate of bilateral neck exploration of 54% but no difference in multiglandular disease between the classic pHPT, ncHPT and nhHPT groups. The reported use of bilateral neck exploration in patients with nhHPT varies (50%–91%), but because many surgeons use it as the standard initial operative approach, it is difficult to extrapolate its correlation to multiglandular disease.

Limitations

Although our study is limited by its retrospective nature, the fact that it combined patient populations from 2 North American cities may have helped overcome some inherent biases. The reported upper limit of normal for PTH varies between 40 pg/dL and 72 pg/dL, reflecting different assays used in different centres. The upper limit of normal used in this study, 65 pg/dL, represents the threshold for normal in the majority of patients and an approximate median of values reported in the literature. However, the specific PTH value is less important than the recognition that patients with normal or slightly elevated PTH levels can still be candidates for parathyroidectomy guided by intraoperative PTH monitoring. The accuracy of preoperative localization studies was not available in this data set and would be an area of interest in subsequent analysis. Although patients were followed for at least 6 months, this interval may not have been long enough to detect recurrent hyperparathyroidism. Future studies would ideally have a larger sample of patients with nhHPT, with prospective data collection and long-term follow-up. Finally, recognizing that PTH levels can be influenced by multiple variables, it would be beneficial to have creatinine and vitamin D levels to compare between patient populations.

CONCLUSION

A decrease of more than 50% in PTH level during parathyroidectomy in patients with nhHPT accurately predicted operative success at a mean follow-up duration of 13.6 months. However, the rate of decrease in PTH level in this group was slower than that in patients with classic pHPT, which suggests that PTH measurement at 20 minutes may be required to observe a decrease of more than 50% in patients with nhHPT. Intraoperative PTH monitoring may also help identify multiglandular disease in patients with nhHPT, using criteria similar to those in classic pHPT, with comparable operative success.

Affiliations: From the Division of Surgical Oncology, DeWitt Daughtry Family Department of Surgery, Leonard M. Miller School of Medicine, University of Miami, Miami, Fla. (Stuart, Azab); the Division of Surgical Oncology, Department of Surgery, University of British Columbia, Vancouver, BC (Stuart); the Division of Endocrine Surgery, DeWitt Daughtry Family Department of Surgery, Leonard M. Miller School of Medicine, University of Miami, Miami, Fla. (Picado Roque, Lew); and the Division of Surgical Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alta. (Pasieka).

Competing interests: None declared.

Contributors: B. Azab, J. Pasieka and J. Lew designed the study. B. Azab, O. Picado Roque, J. Pasieka and J. Lew acquired the data, which all authors analyzed. H. Stuart, B. Azab, J. Pasieka and J. Lew wrote the manuscript, which B. Azab, O. Picado Roque, J. Pasieka and J. Lew critically revised. All authors gave final approval of the article to be published.

Content licence: This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) licence, which permits use, distribution and reproduction in any medium, provided that the original publication is properly cited, the use is noncommercial (i.e., research or educational use), and no modifications or adaptations are made. See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Yeh MW, Ituarte PHG, Zhou HC, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab 2013;98:1122-9.
2. Silverberg SJ, Bilezikian JP. Evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab 1996;81:2036-40.
3. Hollenberg AN, Arnold A. Hypercalcemia with low-normal serum intact PTH: a novel presentation of primary hyperparathyroidism. JAMA Surg 1998;165:197-8.
4. Glendenning P, Gutteridge DH, Retallack RW, et al. High prevalence of normal total calcium and intact PTH in 60 patients with proven primary hyperparathyroidism: a challenge to current diagnostic criteria. Aust N Z J Med 1999;28:173-8.
5. Glendenning P, Pullan PT, Gulland D, et al. Surgically proven primary hyperparathyroidism with a suppressed intact parathyroid hormone. Med J Aust 1996;165:197-8.
6. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons guidelines for definitive management of primary hyperparathyroidism. JAMA Surg 2016;151:959-68.
7. Irvin GL 3rd, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. *World J Surg* 2004;28:1287-92.

8. Amin AL, Wang TS, Wade TJ, et al. Normal PTH levels in primary hyperparathyroidism: Still the same disease? *Ann Surg Oncol* 2011;18: 3437-42.

9. Lafferty FW, Hamlin CR, Corrado KR, et al. Primary hyperparathyroidism with a low-normal, atypical serum parathyroid hormone as shown by discordant immunoassay curves. *J Clin Endocrinol Metab* 2006;91:3826-9.

10. Wallace LB, Parikh RT, Ross LV, et al. The phenotype of primary hyperparathyroidism with normal parathyroid hormone levels: How low can parathyroid hormone go? *Surgery* 2011;150:1102-12.

11. Mischis-Toussard C, Goudet P, Verges B, et al. Primary hyperparathyroidism with normal serum intact parathyroid hormone levels. *QJM* 2000;93:365-7.

12. Bergenfelz A, Lindblom P, Lindergård B, et al. Preoperative normal level of parathyroid hormone signifies an early and mild form of primary hyperparathyroidism. *World J Surg* 2003;27:481-5.

13. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab* 2014;99:3561-9.

14. Lowe H, McMahon DJ, Rubin MR, et al. Normocalcemic primary hyperparathyroidism: further characterization of a new clinical phenotype. *J Clin Endocrinol Metab* 2007;92:3001-5.

15. Perez JB, Pazianos AG. Unusual presentation of primary hyperparathyroidism with osteoporosis, hypercalcemia, and normal parathyroid hormone level. *South Med J* 2001;94:339-41.

16. Khan AA, Hanley DA, Rizzoli R, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporos Int* 2017; 28:1-19.

17. Irvin GL 3rd, Sfakianakis G, Yeung L, et al. Ambulatory parathyroidectomy for primary hyperparathyroidism. *Arch Surg* 1996;131: 1074-8.

18. Carneiro DM, Solorzano CC, Nader MC, et al. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: Which criterion is the most accurate? *Surgery* 2003;134:973-9, discussion 979-81.

19. Javid M, Callender G, Quinn C, et al. Primary hyperparathyroidism with normal baseline intraoperative parathyroid hormone: a challenging population. *Surgery* 2017;161:493-8.

20. Applewhite MK, Schneider DF. Mild primary hyperparathyroidism: a literature review. *Oncologist* 2014;19:919-29.

21. Alhefidi A, Pinchot SN, Davis R, et al. The necessity and reliability of intraoperative parathyroid hormone (PTH) testing in patients with mild hyperparathyroidism and PTH levels in the normal range. *World J Surg* 2011;35:2006-9.

22. Trinh G, Noureldine SI, Russell JO, et al. Characterizing the operative findings and utility of intraoperative parathyroid hormone (IOPTH) monitoring in patients with normal baseline IOPTH and normohormonal primary hyperparathyroidism. *Surgery* 2017;161: 78-86.

23. Graves CE, McManus CM, Chabot JA, et al. Biochemical profile affects IOPTH kinetics and cure rate in primary hyperparathyroidism. *World J Surg* 2020;44:488-95.

24. Khan ZF, Picado O, Marcadi AR, et al. Additional 20-minute intraoperative parathormone measurement can minimize unnecessary bilateral neck exploration. *J Surg Res* 2019;235: 264-9.

25. Carneiro-Pla DM, Irvin GL 3rd, Chen H. Consequences of parathyroidectomy in patients with “mild” sporadic primary hyperparathyroidism. *Surgery* 2007;142:795-9, discussion 799-e1-2.

26. Kirakopoulos A, Petrarias A, Linos D. Classic primary hyperparathyroidism versus normocalcemic and normohormonal variants: Do they really differ? *World J Surg* 2018;42:992-7.