Intraoperative Parathyroid Hormone Assay

An Accurate Predictor of Symptomatic Hypocalcemia Following Thyroidectomy

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Hypothesis: Intraoperative parathyroid hormone (IOPTH) assay is useful for predicting symptomatic hypocalcemia following total thyroidectomy.

Design: A prospective study of 30 patients undergoing total thyroidectomy with IOPTH levels obtained following skin closure and ionized calcium (Ca\(^{2+}\)) levels obtained 6 hours postoperatively and on postoperative day 1. All patients were evaluated for symptoms of hypocalcemia.

Setting: University teaching hospital.

Main Outcome Measures: Patients who developed symptomatic hypocalcemia were compared with asymptomatic patients in regard to age, diagnosis, thyroid weight, thyrotropin level, Ca\(^{2+}\) level, parathyroid status, and IOPTH level.

Results: The onset of symptomatic hypocalcemia ranged from 8 to 48 hours postoperatively (n=10). One patient required readmission. Of 10 patients with symptoms, 5 developed tetany. There were no significant differences in age, diagnosis, thyroid weight, thyrotropin level, or the number of parathyroid glands preserved in patients with or without symptomatic hypocalcemia. All patients with an IOPTH level of less than 10 pg/mL (1.1 pmol/L) had symptoms (n=8). The mean±SD IOPTH level (7.6±12.0 pg/mL [0.8±1.3 pmol/L]) in patients who developed symptomatic hypocalcemia was significantly lower than the mean IOPTH level (55.7±31.8 pg/mL [5.9±3.3 pmol/L]) in patients without symptoms (P=.001). The 6-hour and postoperative day 1 Ca\(^{2+}\) levels were significantly lower in patients with symptomatic hypocalcemia (P=.19 and P=.13, respectively). An IOPTH level of less than 10 pg/mL is 80% sensitive and 100% specific for the development of symptomatic hypocalcemia.

Conclusion: The incorporation of the IOPTH assay in the management of thyroid disease is recommended to prevent and prospectively treat symptomatic hypocalcemia, thereby reducing readmissions following thyroidectomy.

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Despite meticulous surgical dissection, the most common complication following total thyroidectomy is hypocalcemia secondary to hypoparathyroidism.\(^1\) The development of hypocalcemia is likely multifactorial, secondary to parathyroid devascularization, injury, inadvertent removal of the parathyroid, “stunning” from dissection, or hemodilution. Although complications such as recurrent laryngeal nerve injury and cervical hematoma most often occur within 24 hours postoperatively, the symptoms of hypocalcemia may not occur for several days.\(^2\) This delay in diagnosis has challenged clinicians and has prompted many to advocate prolonged hospitalization to monitor serum calcium levels, thus potentially preventing readmissions for symptomatic hypocalcemia.

Even with a delay in the manifestation of symptomatic hypocalcemia, current health care practices have led to shorter hospitalizations for thyroid operations. Many patients are being discharged on the day of the procedure or within 24 hours postoperatively, with minimal morbidity and mortality. However, with reports of up to an 87% incidence of hypocalcemia following total thyroidectomy, this short-stay thyroid surgery must be carefully analyzed in order to maintain the quality of care and minimize complications.\(^3\) To minimize complications and allow for early discharge, we must be able to identify the cohort of patients who will develop symptoms of hypocalcemia. Those patients not at risk would be candidates for early discharge. Those identified as at risk could begin taking calcium and vitamin D supplementa-
This study prospectively evaluated the use of IOPTH levels as a predictor of symptomatic hypocalcemia. Thirty patients (28 women and 2 men; mean age, 38.8 years) undergoing total thyroidectomy from July 2001 through June 2002 were studied. All patients had preoperative serum calcium levels within the reference range. The IOPTH levels were obtained following skin closure using the Immulite automated immunoassay analyzer (Diagnostic Products Corp, Los Angeles, Calif). Ionized calcium (Ca\(^{2+}\)) levels were obtained at 6 hours postoperatively and postoperative day 1. Patients with IOPTH levels of less than 10 pg/mL (reference range, 12-72 pg/mL [1.3-7.6 pmol/L]) began taking oral calcium supplements (1500 mg of elemental calcium daily). All patients were clinically evaluated for signs and symptoms of hypocalcemia. Patients who developed tetany were treated with intravenous calcium in addition to oral supplementation.

Patients who developed symptoms of hypocalcemia were then compared with asymptomatic patients in regard to age, diagnosis, thyroid weight, thyrotropin level, postoperative Ca\(^{2+}\) level, parathyroid status, and IOPTH level. An undetectable IOPTH level was assigned a value of 1 pg/mL for statistical analysis. The number of parathyroid glands preserved was determined by gross evaluation. Parathyroid glands that were autotransplanted were not considered preserved. Statistical analysis was performed with commercially available statistical software (Statistical Product and Service Solutions, version 10.0; SPSS Inc, Chicago, Ill).

Ten of 30 patients undergoing total thyroidectomy developed symptoms of hypocalcemia. All symptomatic patients were women (mean ± SD age, 33.5 ± 11.3 years). The onset of symptoms occurred from 8 to 48 hours postoperatively (mean, 20.4 hours). Five of these patients developed tetany and required intravenous calcium in addition to oral calcium supplementation. Two of 7 patients who underwent parathyroid autotransplantation developed symptomatic hypocalcemia, and both of these patients required intravenous calcium.

The 10 patients with symptomatic hypocalcemia are compared with the 20 asymptomatic patients in the Table. A 2-tailed t test failed to identify any significant differences in age, thyrotropin level, the number of parathyroid glands preserved, and thyroid gland weight in patients with or without symptomatic hypocalcemia. The mean ± SD IOPTH level (7.6 ± 12.0 pg/mL [0.8 ± 1.3 pmol/L]) in patients who developed symptomatic hypocalcemia was significantly lower than the mean IOPTH level (55.7 ± 31.8 pg/mL [5.9 ± 3.3 pmol/L]) in patients without symptoms (P < .001). All patients with an IOPTH level of less than 10 pg/mL had symptoms (n = 8). An IOPTH level of less than 10 pg/mL had a sensitivity of 80%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 91% for the development of symptomatic hypocalcemia.

At 6 hours postoperatively, 27 (96%) of 28 patients had a Ca\(^{2+}\) level below the reference range (1.15-1.27 mmol/L). On postoperative day 1, 27 (93%) of 29 patients had a Ca\(^{2+}\) level below the reference range. The 6 hours postoperatively and postoperative day 1 Ca\(^{2+}\) levels were significantly lower in patients with symptomatic hypocalcemia (0.97 vs 1.07 mmol/L and 0.99 vs 1.07 mmol/L; P = .19 and P = .13, respectively). There was a significant positive correlation between both the 6-hour and postoperative day 1 Ca\(^{2+}\) levels and IOPTH level (P = .03 and P = .01, respectively). A Ca\(^{2+}\) level of less than 1.0 mmol/L obtained 6 hours postoperatively had a sensitivity of 40%, a specificity of 94%, a positive predictive value of 80%, and a negative predictive value of 74% for the development of symptomatic hypocalcemia. A Ca\(^{2+}\) level of less than 1.0 mmol/L obtained on postoperative day 1 had a sensitivity of 50%, a specificity of 79%, a positive predictive value of 56%, and a negative predictive value of 75% for the development of symptomatic hypocalcemia.

Overall, 27 patients were discharged within 24 hours of their operation. Two patients had hospital stays of 2 days and 3 days because they required intravenous calcium to control their symptoms until they received adequate oral calcium and vitamin D supplementation. A third patient with papillary thyroid carcinoma was diagnosed with familial polyposis and hospitalized for 13 days for parenteral nutrition. This patient had mild paresthesias that did not necessitate intravenous calcium. The patient who had symptoms of hypocalcemia at 48 hours postoperatively required readmission and intravenous calcium. This patient had an IOPTH level of 31 pg/mL (3.3 pmol/L), and on readmission, the intact parathyroid hormone (iPTH) level was 2 pg/mL (0.2 pmol/L). One other patient had an IOPTH level of more than 10...
pg/mL (29 pg/mL [3.1 pmol/L]) and symptoms of paresthesias. This patient developed symptoms 24 hours postoperatively, took calcium supplementation at home for 3 days, and was normocalcemic at 2 weeks postoperatively. The 5 most recent patients with IOPTH levels of less than 10 pg/mL received both oral calcium and vitamin D supplementation. None of these patients required intravenous calcium.

Final pathologic diagnoses were multinodular goiter (10 patients), papillary thyroid carcinoma (5 patients), Graves disease (5 patients), follicular adenoma (5 patients), Hashimoto thyroiditis (4 patients), and lymphoma (1 patient). Pearson χ² analysis of the pathologic diagnoses for patients with benign (non-Graves), malignant, and Graves disease did not identify a significant association with the development of symptomatic hypocalcemia (P = .94).

All patients were seen in follow-up. Of the 10 patients with symptomatic hypocalcemia, 2 patients continued to receive calcium supplementation at 9 months and 10 months postoperatively. One of these patients had an iPTH level of 12 pg/mL (1.3 pmol/L) and the other had an undetectable iPTH level.

The results of this study show that IOPTH levels can predict in a reliable and timely fashion which patients will develop symptomatic hypocalcemia following thyroidectomy. Although serum calcium levels may correlate with the development of symptomatic hypocalcemia, these results are often not useful until 12 or 24 hours postoperatively. This delay can postpone therapy and prolong hospitalizations. In contrast, the use of IOPTH levels provides the surgeon with a very sensitive (80%) and highly specific (100%) tool for predicting which patients may develop symptomatic hypocalcemia before they leave the operative suite. With a positive predictive value of 100% and a negative predictive value of 91%, an IOPTH level of less than 10 pg/mL can be used to determine whether patients require early calcium and vitamin D supplementation and predict a safe and early hospital discharge.

The use of IOPTH levels during thyroid surgery was also recently reported by Lindblom et al.8 These investigators compared IOPTH levels in 38 patients undergoing near-total or total thyroidectomy, with or without biochemical and symptomatic hypocalcemia. Their results were similar to ours in that an IOPTH level below the reference range and a postoperative day 1 serum calcium of less than 8 mg/dL (2 mmol/L) both predicted symptomatic hypocalcemia, with the IOPTH being more sensitive and specific (71% vs 52% and 81% vs 76%). An IOPTH level below the reference range identified 12 (71%) of 17 patients with symptomatic hypocalcemia, compared with 8 (80%) of 10 patients in the current study. The improved sensitivity and specificity in our study (80% vs 71% and 100% vs 81%) may have resulted from different assays and reference ranges. The Elecsys 2010 assay (Roche Diagnostics, Indianapolis, Ind) used in their study had a reference range of 1.6 to 6.9 pmol/L (15-66 pg/mL) compared with the Immulite assay reference range of 12 to 72 pg/mL (1.3-7.6 pmol/L).

It is feasible that the sensitivity may be improved with a delay in obtaining the PTH level or by measuring sequential PTH levels. Warren et al9 measured PTH levels immediately postoperatively (IOPTH) and in the recovery room in 17 patients who underwent total thyroidectomy. In their study, no patient with an IOPTH level of more than 15 pg/mL (1.6 pmol/L) developed hypocalcemia (defined as symptoms or an ionized calcium level of less than 1.0 mmol/L). Four patients had IOPTH levels of less than 15 pg/mL. Three of these patients had increased PTH levels in the recovery room, and 1 patient had a stable PTH level. One patient with an increasing recovery PTH level and the patient with a stable PTH level both developed hypocalcemia. Although their patient population is small, their results do suggest that a PTH level obtained after the patient has left the recovery room may more accurately predict hypocalcemia.

In our study, the number of parathyroid glands preserved in situ was not an accurate predictor of symptomatic hypocalcemia. Similar findings were reported by Bergamaschi et al.10 In their study, 731 patients underwent bilateral thyroid resections, and there was no correlation between the number of parathyroid glands identified and postoperative calcium levels. However, they did find that the rates of hypoparathyroidism increased in patients who had parathyroid glands autotransplanted during total thyroidectomy. In our study, most patients (5/7) undergoing parathyroid autotransplantation remained asymptomatic. In contrast, Glinoer et al11 found a linear correlation between the number of parathyroid glands preserved and the development of early hypocalcemia (within 1 week) in 82 patients undergoing bilateral thyroid lobectomies. However, the overall predictability for symptomatic hypocalcemia was limited, because they reported severe hypocalcemia in 20% of patients with 1 or 2 parathyroid glands preserved, in 9% of patients with 3 parathyroid glands preserved, and in 3% of patients with 4 parathyroid glands preserved. Neither of our studies found a significant relationship between hypocalcemia and patient age, thyroid gland weight, or thyroid function status.

Although many risk factors may be associated with the development of symptomatic hypoparathyroidism, to date there is no factor more predictive and clinically useful than the IOPTH assay. In addition to clinical utility, the IOPTH assay also may be cost-effective. At our institution, the Immulite IOPTH assay costs 3 times as much as an ionized calcium level ($156 vs $55). However, the use of the IOPTH assay reduces the need to obtain sequential calcium levels. The equivalence in cost between 1 IOPTH assay and 3 sequential calcium levels in association with the possibility of a shorter hospitalization and an excellent prediction of symptomatic hypocalcemia make the postthyroidectomy PTH assay an economic and clinically useful test.

In times of early patient discharge, the incorporation of the IOPTH assay into the management of thyroid disease is recommended to prevent and prospectively treat...
symptomatic hypocalcemia, thereby reducing readmissions following thyroidectomy.

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REFERENCES


DISCUSSION

Jon van Heerden, MD, Rochester, Minn: Thyroid surgery as done by experienced endocrine surgeons is currently one of the safest operations performed. An increasing number of thyroid resections are being performed through limited collar incisions where the current surgical philosophy appears to be, “mine is smaller than yours.” The operation has in essence a 0% operative mortality and a morbidity rate of less than 1%. Many of these resections, as Dr Richards said, are being performed under regional or local anesthesia and on an ever-increasing outpatient basis, with the patients being dismissed within hours of the operation.

Principal postthyroidectomy morbidities are basically 2-fold, recurrent nerve palsies or paresis and hypocalcemia, which might be permanent or temporary. Although the former should be a rarity in experienced hands, the latter remains problematic and has gained increasing importance with a trend towards decreased length of hospitalization, especially outpatient surgery. As you know, the measurement of postresection serum calcium levels is an accurate predictor of hypocalcemia. Unfortunately the decline in serum calcium levels is slow, and the low nadir may not be reached until 24 to 30 hours post-thyroidectomy, a fact which I am sure you will agree negates early hospital dismissal unless routine calcium is administered following thyroid resection, total thyroidectomy in particular.

Dr Richards and her colleagues have documented a short-cut to the determination of postthyroidectomy hypocalcemia by reminding all of us of the physiological principal that the half life of PTH is a mere 2.5 minutes and that its measurement is a very accurate predictor of subsequent hypocalcemia. The message I believe is an excellent one indeed and is one that can shorten and improve the postoperative course of patients undergoing total thyroidectomy.

Parathyroid hormone measurement is easy to do, is widely available, and is highly accurate. For the past 5 years or so, PTH measurements have become the routine in our practice in all patients following total thyroidectomy. It has allowed us to make much earlier decisions about the need for postoperative calcium replacement in comparison to the era where we relied on the determination of serum calcium alone. Those patients were often in the hospital for 3, 4, or 5 days.

My congratulations to Dr Richards and the coauthors, for whom I have a few minor questions. Have you and your group performed subsequent PTH determinations to analyze the PTH trend? In other words, how long may viable parathyroid glands be “stunned” and thus physiologically inactive? What is your long-term management of those patients who have been placed on calcium in the early postoperative period? What is the authors’ philosophy regarding parathyroid autotransplantation during thyroidectomy? And, lastly, do the authors utilize the rapid, or the so-called, quick, PTH determination or the more conventional PTH assay?

Richard A. Prinz, MD, Chicago, Ill: This study looks at a technology that is available but expensive, so we have to ask, do we really need to measure parathyroid hormone intraoperatively when performing thyroidectomy? I am struck by the very high rate of postoperative hypocalcemia in this series. A third of the patients had symptomatic hypocalcemia, and, remarkably, 5 patients required intravenous calcium, which is very very high in my experience. So to flip this around, I would say if your rates of this problem are that high, should you not be just routinely treating these patients for hypocalcemia?

We have used this technique first when we were doing parathyroid surgery because about 10% to 15% of our patients with hyperparathyroidism will have an associated thyroid problem that requires thyroidectomy. Have you had any experience using intraoperative PTH levels in hyperparathyroid patients who also require concomitant thyroidectomy?

I would like to get back to how you manage the patients who have a quick PTH value of less than 10 pg/mL. Do you keep them in the hospital for added days now, because that is extremely difficult with managed care constraints today?

Peter Angelos, MD, Chicago: This is a really nice paper and brings us to a technique that we have used in parathyroid surgery that may have wider use in thyroid surgery. I have a couple of questions. Echoing Dr Prinz’s comments, can you give us some sense of how much additional this costs patients and whether you have any sense of how much earlier you are able to discharge them from the hospital. Second, does this change your practice? In other words, if you get a PTH level that is less than 10 pg/ml, do you know that while you are in the operating room? Can you do different things, like look at the parathyroids, perhaps autotransplant one, that sort of thing? Finally, I am just curious for your comments on an alternative approach, which we have used and have previously reported. We check an ionized calcium level 8 hours postoperatively and have used that as a predictor of who needs oral calcium on discharge. In our experience, that one value predicted greater than 90% of patients who developed symptomatic hypocalcemia.
Dr Richards: Dr van Heerden’s first question regarding subsequent PTH values: 7 of these 10 patients did have PTH values obtained in follow-up. Initially, there were 3 patients who had undetectable PTH values, and at 4-weeks’ follow-up, these patients had PTH levels of 12, 18, and 19 pg/mL. There was 1 patient who had an undetectable PTH value, and at 10 months’ follow-up, this patient continues to have an undetectable PTH. Two patients had intraoperative PTH levels of 3 and 7 pg/mL, which had increased to 5 and 16 pg/mL by 4 weeks of follow-up. A seventh patient had an intraoperative PTH of 31 pg/mL that was down to 2 pg/mL at 48 hours postoperatively and by 4 weeks was 36 pg/mL. Therefore, all of the patients who did discontinue or reduce their calcium had increases in the PTH values by 4 weeks. So while the intraoperative PTH may not predict which patients developed transient vs permanent hypoparathyroidism, a 4-week intact PTH may be a better predictor of which patients will fall into each category.

We manage the patients’ postoperative calcium supplementation with a combination of both clinically and biochemically. Ideally, we aim to maintain the calcium levels at a low range in order to stimulate parathyroid activity, yet have an asymptomatic patient. In patients who have normal vitamin D levels, the calcium is increased according to their symptoms. If a patient is requiring an extraordinarily large amount of calcium, over 2 g/d, serum calcium, PTH, vitamin D levels, and urinary calcium levels are measured. If the urinary calcium is high, we may start these patients on a thiazide diuretic to increase calcium resorption. For patients on calcium supplementation who are asymptomatic, we generally taper them over time in concordance with their symptoms.

As to the role of parathyroid autotransplantation in our practice, the parathyroid glands are identified with gross inspection. If there is a parathyroid gland that has questionable viability, it is immediately minced and immediately implanted in the sternocleidomastoid, assuming the patient does not have hyperparathyroidism. We may occasionally send a biopsy specimen if we want assurance that what we are implanting is indeed a parathyroid gland and not lymph node metastases.

Dr van Heerden’s fourth question: whether we use the rapid or conventional intact PTH. For parathyroid surgery, we will use the rapid or turbo PTH. For thyroid surgery, we use the conventional PTH, but we are running these within an hour after the case. This provides results while the patient is in the recovery room and reduces the likelihood of a falsely low PTH. The turbo assay is a little more sensitive at lower PTH levels. The turbo PTH values tend to be a little higher in the higher ranges. Overall, with the increased sensitivity in the low range, both the turbo or the conventional PTH can be used to predict hypocalcemia.

Dr Prinz addressed the issue of cost. I am a very cost-conscious person. The Nichols assay, which was initially available, was very expensive, about $1000 a patient. Therefore, I waited for a cheaper assay for parathyroid surgery because the amount of time it took for a bilateral exploration did not justify the additional cost. The Immulite assay has brought the cost down to about $60 a patient at our hospital—a very inexpensive test for what we gain.

Five patients did require intravenous calcium. Whether these patients had severe symptoms or not may be in question. At a teaching hospital, the residents may treat patients with mild paresthesias with intravenous calcium. I am generally one to go ahead and try to push the per os calcium and vitamin D because there is significantly more elemental calcium with those modalities.

Our overall permanent rate of hypoparathyroidism was 3%. Most of the literature is at 6%. Why a third of these had symptoms may be a result of direct rather than open-ended questioning. There may have been some people who may have not had significant symptoms if you didn’t ask them about their symptoms.

The other option of treating all patients with calcium was how I managed patients prior to utilizing the intraoperative PTH assay. However, patients who have undetectable PTH levels will require vitamin D in addition to the calcium. By obtaining intraoperative PTH levels, we were able to select out those patients that are going to need vitamin D.

For utilizing the PTH during parathyroid surgery and thyroid surgery, I have not done that because most of the parathyroid surgery is done minimally invasive. By doing it minimally invasive, you may or may not find a thyroid nodule. Occasionally you may have a patient with both thyroid and parathyroid pathology, but I have not had extensive experience using the PTH intraoperatively for those patients.

In terms of days of hospitalization, if the PTH is less than 10 pg/mL, this has not increased the length of hospitalization. It has mainly allowed us to predict which patients are going to need vitamin D so that we can start their calcium and vitamin D supplementation immediately rather than waiting until they have symptoms.

Dr Angelos had addressed the additional cost, which was about $60 with that assay. It does allow for early discharge because these patients can be prospectively treated. Our practice is not changed in the operating room because most of our PTH values are obtained in the recovery room, but even if they weren’t, our clinical practice would still the same. If there is a parathyroid that is questionable, it is autotransplanted rather than trying to judge its viability bases on a low PTH level. Even if the PTH level is low, it can not predict that your parathyroid is not going to gain back its function. A parathyroid gland is probably more likely to gain function if it is left in situ rather than autotransplanted.

Dr Angelos, we referenced your paper on the utilization of ionized calcium levels in our manuscript. The downside of this method is that there is a delay in identifying which patients are going to have low calcium levels. The IOPTH gives you a quicker heads up on the game rather than waiting until the patient may develop symptoms. The other paper that you discussed measured serial calcium levels at approximately 8 hours, 12 hours, and 24 hours and then following the curve. But again, these methods define patients at risk but are not as predictive as the IOPTH.