Streamlining of intra-operative parathyroid hormone measurements for cure during parathyroidectomy

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Abstract

BACKGROUND: The timing of intraoperative parathyroid hormone measurements during parathyroidectomy for the treatment of primary hyperparathyroidism is quite variable. Although a 50% decrease after excision is considered predictive of cure, it is not known which combination of measurements is most useful.

METHODS: Two hundred thirteen patients underwent resection of solitary parathyroid adenomas. Sex, age, intraoperative parathyroid hormone level at baseline, before adenoma removal (T₀), and 5 minutes (T₅) and 10 minutes (T₁₀) after adenoma removal; and 50% decrease were tested for associations with cure.

RESULTS: A 50% decrease in intraoperative parathyroid hormone level was 95% sensitive for cure (95% confidence interval, 89% to 98%) but did not predict cure for individual patients. A decrease into the normal range was not correlated with cure (P = .50). However, a 50% decrease from T₀ to T₁₀ was 97% predictive of cure (odds ratio, 6.5; P = .08).

CONCLUSIONS: The decrease in parathyroid hormone level from T₀ to T₁₀ during parathyroidectomy was most predictive of cure of primary hyperparathyroidism. A decrease into the normal range did not improve the performance characteristics of this test.

Primary hyperparathyroidism is a disease that may present with nephrolithiasis, hypercalcemia, depression, osteopenia, peptic ulcer disease, pancreatitis, or proximal muscle weakness, or it may be totally asymptomatic. Primary hyperparathyroidism has a prevalence of .3% to 1% in the adult population. In 80% to 85% of patients, primary hyperparathyroidism is due to parathyroid hormone hypersecretion from a solitary parathyroid adenoma. Other causes of primary hyperparathyroidism include parathyroid gland hyperplasia (10%), multiple parathyroid adenomas (4%), and parathyroid carcinoma (1%). Given that parathyroidectomy is the only treatment that offers cure of primary hyperparathyroidism, it is currently recommended that affected individuals undergo surgery.

However, surgical resection may be challenging because of difficulties in consistently locating pathological glands by neck exploration alone, which can result in uncertainty.
regarding the completeness of resection and cure. \(^5\) A focused approach for parathyroidectomy utilizes preoperative imaging and intraoperative parathyroid hormone measurements to limit the extent of surgical exploration but ensure cure. There is debate regarding which intraoperative parathyroid hormone measurements best confirm cure after the removal of abnormal parathyroid glands. The gold standard for the cure of primary hyperparathyroidism is an enduring normalization of serum calcium levels postoperatively, but there is currently no accepted worldwide standard for intraoperatively confirming cure during parathyroidectomy.\(^5,7,9\)

Historically, bilateral neck exploration with examination of all 4 parathyroid glands to identify and remove grossly abnormal glands was the gold-standard approach during parathyroidectomy.\(^5,10\) Recently, a more focused approach, in which preoperative imaging guides surgical exploration and intraoperative parathyroid hormone measurement confirms cure, has become commonly used. A 50% decrease in the parathyroid hormone level from the baseline level (before the skin incision) or adenoma excision (T0) to 5, 10, or 30 minutes after pathological parathyroid removal is generally accepted as being predictive of a successful operation and is termed “biologic recovery.”\(^11\) However, this testing may significantly lengthen the duration of surgery because of laboratory processing time, and it may also be unreliable, with low negative predictive values that can range from 15% to 60% depending upon the timing of parathyroid hormone measurement.\(^12,13\) Thus, there is an ongoing search for more sensitive, timely, and cost-effective methods of predicting successful resection of abnormal parathyroid glands during parathyroidectomy.

Computed tomographic (CT) sestamibi or hybrid single-photon emission CT/CT scans have sensitivity of 93% and a specificity of 99% for localizing parathyroid adenomas,\(^9\) and their performance has been improving.\(^14,15\) Additionally, high-resolution ultrasound has a similar level of sensitivity and specificity for localizing abnormal parathyroid glands if the sonographer is experienced in parathyroid imaging.\(^7\) Focused parathyroid operations, guided by preoperative imaging, along with intraoperative parathyroid hormone measurements, have largely replaced routine bilateral neck exploration.\(^16,17\) This is particularly true if both nuclear medicine scans and ultrasound imaging concordantly localize a solitary abnormal parathyroid gland. Additionally, the use of radiologic guidance during parathyroidectomy with gamma detection devices, 4-dimensional computed tomography or magnetic resonance imaging for preoperative parathyroid adenoma localization, has also been increasing.\(^2\)

However, the current literature suggests that 4-gland parathyroid exploration is still required for 20% to 40% of patients with equivocal results on preoperative imaging. The use of intraoperative parathyroid hormone measurement is particularly useful for this group that does not localize preoperatively, as well as in circumstances in which surgical uncertainty exists regarding the removal of pathologic parathyroid glands.\(^3\) The objective of this prospective cohort study was to determine which intraoperative parathyroid hormone measurements best correlate with cure of primary hyperparathyroidism after the removal of a solitary parathyroid adenoma. The results may allow a reduction in the number of intraoperative parathyroid hormone measurements, potentially reducing operative time, complexity, and cost. Additionally, this work may help guide future research into the development of a standardized intraoperative parathyroid hormone measurement protocol that best predicts cure.

**Methods**

In this prospective cohort study, data were collected from 293 sequential patients undergoing their initial operation for removal of a suspected solitary parathyroid adenoma for treatment of primary hyperparathyroidism between 2004 and 2011 at St Paul’s Hospital (Vancouver, BC, Canada). The preoperative diagnosis of a parathyroid adenoma was made on the basis of preoperative elevations of calcium and parathyroid hormone levels, in combination with imaging suggesting the localization of a solitary adenoma. This study was carried out with approval of our institutional research ethics board. All patients underwent preoperative parathyroid localization imaging with combined noncontrast single-photon emission CT/CT as well as ultrasound, had intraoperative frozen section of tissues removed, and had their postoperative serum or ionized calcium levels measured before their discharge from the hospital (usually the day of surgery or 1 day postoperatively). When available, calcium levels were measured at follow-up visits at a time interval that was longest after the date of parathyroidectomy. These calcium levels were then used to determine postoperative disease status (cured or not cured) for each patient. Seventy-five percent of postoperative calcium levels were measured between 9 and 138 days postoperatively (range, 1 to 1,070 days), and cure was defined as normalization of the serum or ionized calcium level postoperatively.

**Laboratory methods**

Serum total calcium and intact parathyroid hormone determinations used in initial screening and diagnosis varied according to the routine methods used in the referral catchment of St Paul’s Hospital. Postoperative total calcium determinations were performed using the Siemens Advia 1650 and the Siemens Advia 1800 clinical chemistry analyzer (Siemens Healthcare, Erlangen, Germany) using the o-cresolphthalein method and, subsequently, the arsenazo III method. Ionized calcium determinations were performed using the Radiometer ABL 700 and ABL 800 series of blood gas analyzers. Intraoperative intact parathyroid hormone determinations were performed on the Roche Elecsys 1010 and the Roche Cobas e411 (Roche Diagnostics GmbH, Mannheim, Germany) using a rapid 2-site
had T0 levels, 92% had T5 levels, and 100% had T10 levels.

All patients had baseline levels, 88% 59 years; range, 19 to 89 years) was consistent with 75% female and 25% male, with an age distribution (mean, able, or they had undergone reoperations, leaving 213 operative parathyroid hormone level measurements available for evaluation. Gender; age; parathyroid hormone levels at baseline, T0, T5, and T10; and whether a 50% decrease in their parathyroid hormone levels at the T10 measurement interval occurred, were tested for their correlations with and prediction of cure using the R statistical programming language (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria) through the R-Studio interface. McNemar’s chi-square test was used to determine whether a 50% decrease in parathyroid hormone levels at various times was associated with cure, and 2 × 2 contingency tables were used to determine the strength of association, measured as odds of cure (odds ratio). These statistical results were used to describe the correlation of parathyroid hormone values with cure for the study group as a whole. Logistic regression analysis was then used to determine if a 50% decrease for a specific combination of measurement time intervals was predictive of cure: baseline to T5 or T10 and T0 to T5 or T10. Although none of the time intervals were predictive of cure with 95% confidence, the T0-to-T10 parathyroid hormone level decrease was most statistically significantly predictive of cure, with 93% confidence (98% predictive of cure; odds ratio, 6.5; P = .08).

Table 1 shows that the parathyroid hormone measurement intervals with the highest sensitivity and positive predictive value for cure were baseline to T10 and T0 to T10. Overall, the best timing of parathyroid hormone measurements was at T0 and T10. This group contained the largest proportion of patients achieving a 50% decrease in parathyroid hormone level with a high cure rate (96%). Additionally, the sensitivity of 87% was better than the performance of other intervals,

### Table 1 Statistical analysis of 50% decrease in parathyroid hormone level by time measurement interval

<table>
<thead>
<tr>
<th>Parathyroid hormone measurement interval</th>
<th>50% decrease</th>
<th>Cure</th>
<th>Sensitivity (%)</th>
<th>Negative predictive value (%)</th>
<th>Positive predictive value (%)</th>
<th>McNemar’s chi-square</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to T5</td>
<td>81/109 = 74%</td>
<td>107/110 = 98%</td>
<td>74</td>
<td>0</td>
<td>98</td>
<td>18</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Baseline to T10</td>
<td>98/115 = 85%</td>
<td>110/115 = 96%</td>
<td>85</td>
<td>6</td>
<td>96</td>
<td>6</td>
<td>.01</td>
</tr>
<tr>
<td>T5 to T10</td>
<td>67/101 = 66%</td>
<td>98/101 = 97%</td>
<td>67</td>
<td>6</td>
<td>98</td>
<td>27</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>T5 to T10</td>
<td>89/104 = 86%</td>
<td>100/104 = 96%</td>
<td>87</td>
<td>13</td>
<td>98</td>
<td>6.7</td>
<td>.01</td>
</tr>
</tbody>
</table>

Of the 213 study patients evaluated, 14 (6%) did not have a 50% decreases in their parathyroid hormone levels at the T10 measurement. These patients all underwent 4-gland neck exploration with the intent of identifying multiglandular disease or hyperplasia. Twenty-five percent of the study patients did not have normal-range parathyroid hormone levels at their T10 measurements, but only 4% of these patients had abnormal postoperative serum calcium levels. Therefore, 84% of those individuals whose parathyroid hormone levels did not normalize intraoperatively still underwent curative operations. Additionally, a decrease of the parathyroid hormone level into the normal range was not found to correlate with cure from primary hyperparathyroidism (P < .05). A 50% decrease in the parathyroid hormone level at any time was found to be 95% sensitive for cure (95% confidence interval, 89% to 98%) but in itself was not predictive of cure for individual patients (Gstat = .454, P = .50). Given the finding that a 50% decrease in parathyroid hormone did not predict cure, logistic regression analysis was used to determine if a 50% decrease for a specific combination of measurement time intervals was predictive of cure: baseline to T5 or T10 and T0 to T5 or T10. Although none of the time intervals were predictive of cure with 95% confidence, the T0-to-T10 parathyroid hormone level decrease was most statistically significantly predictive of cure, with 93% confidence (98% predictive of cure; odds ratio, 6.5; P = .08).

### Results

The standard surgical approach at our center for the treatment of primary hyperparathyroidism is focused parathyroidectomy, or a unilateral neck exploration guided by preoperative imaging, as well as intraoperative parathyroid hormone measurement at times determined by the surgeon. If an adenoma was not confidently localized preoperatively, there were 2 surgical approaches: either a bilateral neck exploration, or a unilateral neck exploration with confirmation of success by intraoperative parathyroid hormone measurement if the parathyroid adenoma was identified on the initial side explored. Eighty patients were excluded from the study population because they had no intraoperative parathyroid hormone level measurements available, or they had undergone reoperations, leaving 213 patients in the study population. The study population was 75% female and 25% male, with an age distribution (mean, 59 years; range, 19 to 89 years) was consistent with reported primary hyperparathyroidism patient populations.5

At least 2 of 4 parathyroid hormone levels were measured for each patient: baseline (before the skin incision), T0 (immediately before resection of the adenoma), T5 (5 minutes after adenoma resection), and T10 (10 minutes after adenoma resection). All patients had baseline levels, 88% had T0 levels, 92% had T5 levels, and 100% had T10 levels available for evaluation. Gender; age; parathyroid hormone levels at baseline, T0, T5, and T10; and whether a 50% decrease in parathyroid hormone level occurred, were tested for their correlations with and prediction of cure using the R statistical programming language (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria) through the R-Studio interface. McNemar’s chi-square test was used to determine whether a 50% decrease in parathyroid hormone levels at various times was associated with cure, and 2 × 2 contingency tables were used to determine the strength of association, measured as odds of cure (odds ratio). These statistical results were used to describe the correlation of parathyroid hormone values with cure for the study group as a whole. Logistic regression analysis was then used to determine to what extent the variables age, sex, occurrence of a 50% decrease in parathyroid hormone level, and 50% decreases at various times predicted cure for individual patients.

Whereby a test’s sensitivity and specificity describe its performance in a population of patients, logistic regression analysis determines to what extent a particular test result will predict a particular outcome. Here, our aim was to determine which 50% decrease in intraoperative parathyroid hormone level, over which time period, is most predictive of cure for individual patients. If we can be confident that a test result will be predictive of cure for an individual patient, rather than the group, then the intraoperative test result for a particular patient will hold more decision-making power during surgery.
and the negative predictive value was also the highest. Interestingly, 3% of patients who exhibited 50% decreases in their intraoperative parathyroid hormone level did not have normal postoperative calcium measurements and therefore did not meet our study’s definition of cure.

Comments

Intraoperative parathyroid hormone monitoring was first described by Nussbaum et al in 1988 and gained favor in the 1990s with improvements in assay processing times and measurement techniques. There are currently multiple possible protocols, but no established standard for intraoperative parathyroid hormone measurements, for determining successful resection of parathyroid adenomas for the treatment of primary hyperparathyroidism. Until 2000, very little research was available to guide the choice of surgical adjuncts when planning parathyroidectomy, and the standard approach was bilateral neck exploration with intraoperative visual identification and removal of abnormal glands. Improvements in imaging, and thus the ability to preoperatively localize abnormal parathyroid glands, along with the use of intraoperative parathyroid hormone measurements to give reassurance that the abnormal glands had been removed, have allowed for the emergence of a more focused surgical approach. However, it is currently not clear at which time intervals intraoperative parathyroid hormone measurements are most predictive of cure.

We found that the intraoperative parathyroid hormone decrease between T₀ and T₁₀ had the highest sensitivity and positive predictive value for cure of primary hyperparathyroidism. An intraoperative decrease of parathyroid hormone level into the normal range did not improve the performance characteristics of the test. Our results show that when a 50% parathyroid hormone decrease occurs, there is a 95% chance of cure when considering a population of patients, but the occurrence of a 50% decrease does not in itself predict cure for individual patients. Interestingly, despite 93% of patients’ having experienced 50% decreases in their intraoperative parathyroid hormone levels, the overall cure rate was actually higher (96%).

Challenging decisions must be made during those operations in which 50% decreases in intraoperative parathyroid hormone levels do not occur after the removal of parathyroid adenomas. In such cases, should the surgeon continue to explore the ipsilateral or contralateral neck looking for another adenoma or wait longer than 10 minutes and measure another parathyroid hormone level? This decision is generally influenced by preoperative localization studies, patient characteristics, and surgeon experience and therefore judgment regarding the potential presence of multiple adenomas or 4-gland hyperplasia. However, in our study, 62.5% of those individuals (5 of 8) who did not have 50% decreases in their intraoperative parathyroid hormone levels were still cured by the procedure. All of these patients underwent bilateral neck exploration and further removal of abnormal parathyroid glands. Because calcium levels may slowly trend downwards postoperatively, especially when very elevated, those patients who did not have 50% decreases in their intraoperative parathyroid hormone levels, but were surgically deemed to have undergone curative parathyroidectomy, should undergo further investigation before being diagnosed with persistent or recurrent disease and undergoing further evaluation for reoperation.

As shown in Table 1, the cure rate for our study population was consistently high at 96% to 98%, regardless of the timing of parathyroid hormone measurement before and after parathyroid adenoma removal. These cure rates are consistent with reports from other centers that carry out focused parathyroidectomy. It is possible that these cure rates would be even higher if long-term postoperative calcium measurements were available for all patients. These observations suggest that in order to carry out successful parathyroidectomy, in addition to intraoperative parathyroid hormone measurement, factors such as preoperative localization testing and surgeon experience are also important. Further evaluation of those cases in which 50% intraoperative parathyroid hormone decreases did not occur may also elucidate factors that influence cure. Whether the small proportion of patients with primary hyperparathyroidism who are not cured by a focused approach justifies a return to routine bilateral neck exploration is controversial and must be interpreted in the context of surgical volumes at each center.

Regardless of the intraoperative parathyroid hormone assay utilized, and the specific criteria applied for intraoperative cure, any center adopting intraoperative parathyroid hormone measurements must thoroughly evaluate the performance of its entire operating room and laboratory process. This is particularly true because some immunoassays marketed for intraoperative use may take >20 minutes in analytical time alone. After sample transport, centrifugation, and reporting times are considered, the time delay in the operating room, or the time spent waiting for assay results may render the test impractical. Future study regarding the curative and predictive value of intraoperative parathyroid hormone measurements, with a specific focus on patients who are not cured despite 50% decreases in their intraoperative parathyroid hormone levels, seems warranted in order to develop an optimized and more standardized protocol for this commonly utilized intraoperative test.

References

Discussion

Joseph H. Frankhouse, M.D. (Portland, OR): I do not do any head and neck surgery, if you must know, but I found this a pleasant diversion, because this is such a well done paper and practical topic. I am proud enough to admit that I have just enough gray hair to remember that the principle of parathyroid surgery 20 years ago included a skilled surgeon who could find all 4 glands with a bilateral neck dissection. This principle is apparently still necessary, but not nearly as popular as it once was.

I do believe this paper is an extremely important contribution to the literature regarding the best way to precisely use parathyroid hormone (PTH) assay to assess completeness of resection of the parathyroid adenoma. The key elements pointed out include that it is not normalization of the PTH that counts, but rather a 50% drop, and that the 10 minute post resection level is the best one to use. That said, I have several questions for the authors.

1. The T10 level being the key makes sense to me since the half life of parathyroid hormone is about 4 minutes. You state that when the T10 level falls to 50% or less of the T0 level, that this is sensitive for cure, but not predictive. Help us understand why you feel that that is an important point to emphasize and how that influences your conclusions. To me it detracts from what I believe is the main point, unnecessarily weakens the conclusion. In my opinion you still need to explain the concepts of sensitivity/specificity/positive predictive value vs using confidence limits for prediction of cure. For instance if you find that your study does not support prediction of cure, explain why not. Is it a question of the calcium levels chosen for definition of cure or is it a question of number of patients in the study? Either you need to explain why that does not detract from the message, or tell me why it does and how a change of study design or future study may change the results of this.

2. You state that the baseline PTH compared to T10 level is not as good at predicting cure as the T0 to T10. That suggests to me that the act of surgery and anesthesia makes the T0 level higher than the usual baseline level done preoperatively. Why is that?

3. The literature shows that today’s imaging with CT ses-tamibi and ultrasound show sensitivity and specificity around 95% for correctly finding the adenoma. Knowing that, is it really necessary to add the intra-operative PTH when those studies are consistent? What does it add in that scenario besides making us wait for almost 30 minutes post resection? Are you advocating for routine use of this on all cases or select cases?

Should we only be using the intraoperative PTH assay for cases in which the imaging is not clear or the intra-operative findings are somewhat equivocal?

5. In your experience, do you think the intra-operative PTH is more useful than either ultrasound or CT sestamibi? Could or should one of these preoperative tests be eliminated in favor of the PTH?

6. You seem to have quite a range of time from 1 day to over 3 years when the post op calcium level was checked for these patients. Is there a standard acceptance of what defines a curative resection such as normocalcemia at 3 or 6 months post op. Do you think lack of a standard time interval between surgery and calcium level could have affected your results?

Overall this was an enlightening and important piece of work in the surgical management of parathyroid disease.