Hypoparathyroidism After Total Thyroidectomy

A Prospective Study

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Hypothesis: Combined measurement of intact parathyroid hormone (iPTH) and serum calcium (sCa) levels is useful for predicting postoperative hypocalcemia with minimal laboratory effort and low costs.

Design: Prospective analysis of 170 consecutive patients.

Setting: University hospital referral center.

Patients: One hundred seventy patients underwent total thyroidectomy. Defining hypoparathyroidism as albumin-adjusted sCa levels of less than 1.9 mmol/L with or without clinical symptoms or subnormal sCa levels (1.9-2.1 mmol/L) with neuromuscular symptoms, the influences of central lymph node dissection, experience of the surgeon, and parathyroid autotransplantation were observed. We measured the sCa and iPTH levels separately and in combination and the postoperative sCa slope to predict patients who were at risk of hypoparathyroidism.

Main Outcome Measures: Predictive values for iPTH and sCa levels were compared to identify postoperative hypoparathyroidism.

Results: Of the 170 study patients, 41 developed transient hypoparathyroidism and 2 developed permanent hypoparathyroidism. The morphologic features and function of the thyroid gland, central neck dissection, experience of the surgeon, and parathyroid autotransplantation did not influence development of postoperative hypoparathyroidism. The best sensitivity for predicting postoperative hypoparathyroidism was 97.7% for measurement of iPTH levels, and the best specificity was 96.1% for measurement of sCa levels. Negative and positive predictive values reached their best (99.0% and 86.0%, respectively) when we combined sCa and iPTH values.

Conclusions: Patients with iPTH levels of 15 pg/mL or less and sCa levels of 1.9 mmol/L or less are at increased risk of developing postoperative hypoparathyroidism. Measuring iPTH levels 24 hours after total thyroidectomy in combination with sCa levels on the second postoperative day allows the prediction of hypoparathyroidism with a high sensitivity, specificity, and positive predictive value.


With a reported incidence of 1.6% to 50%, postoperative hypocalcemia is the most common and sometimes the most severe complication observed after total thyroidectomy. Therefore patients must undergo close postoperative observation and frequent laboratory evaluations. The reasons for postoperative hypoparathyroidism are devascularization of parathyroid glands during surgery owing to the close proximity of the thyroid capsule, the accidental removal of 1 or more parathyroid gland(s), destruction of the parathyroid glands as a result of lymphadenectomy along the recurrent laryngeal nerve (RLN), or hypoparathyroidism due to hematoma formation.

Clinical and biochemically relevant predictive factors for the development of postoperative transient or permanent hypoparathyroidism, as well as how best to time its prediction, constitute a controversial topic in the literature. Some authors ascribe a high predictive value to intraoperative or early perioperative measurement of parathyroid hormone levels (PTH), challenging the common practice of assessing serum calcium (sCa) levels daily until an increase is observed. Others have suggested that sCa concentrations should be measured only in selected patients or during the initial 24-hour postoperative period.

See Invited Critique at end of article
This study prospectively evaluated the incidence of transient and permanent hypoparathyroidism after total thyroidectomy. The goal was to exert minimal laboratory effort to find a feasible, reasonable, and low-cost strategy for identifying patients at risk of postoperative hypoparathyroidism, thus allowing patients to be discharged early.

LABORATORY EVALUATIONS

According to the prospective protocol, albumin-adjusted total sCa levels were measured preoperatively and once daily from 6 to 7 AM on postoperative days 1 to 4. A commercially available intact PTH (iPTH) assay (Elecsys 1010; Roche Diagnostics, Mannheim, Germany) was used to monitor iPTH levels on postoperative days 1 and 4. Intact PTH levels were determined from the same blood samples as the sCa levels. We measured 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels preoperatively in all patients to exclude vitamin D deficiency. Postoperative hypoparathyroidism was defined by postoperative albumin-adjusted sCa levels of less than 1.9 mmol/L (to convert to milligrams per deciliter, divide by 0.25) (reference range, 2.10-2.60 mmol/L) with or without clinical symptoms of hypocalcemia (neuromuscular irritability including paresthesia, muscle cramps, tetany, or seizures) or subnormal sCa levels (1.9-2.1 mmol/L) with neuromuscular symptoms during the first 4 postoperative days.

Patients with hypoparathyroidism were prescribed 500 to 1000 mg of oral calcium supplements (calcium monohydrate and calcium dicitrate [Maxi-Kalz; Vitriar Pharma, Hamburg, Germany]) and 0.25 µg of vitamin D analogue (calcitriol [Roocalr; Roche Diagnostics]) twice a day independent of their clinical symptoms. Intravenous substitution of calcium therapy was unnecessary in this patient series.

PREDICTORS OF HYPOPARATHYROIDISM

Serum Ca levels measured on postoperative days 1 and 4 correlated with the iPTH levels measured on the same days. Postoperative sCa levels were plotted as a function of time and the slope was defined as an increase or decrease in sCa levels during 2 consecutive measurements within 48 hours after operation (within 24 hours and on the second postoperative day). We calculated the function to evaluate its predictive value for postoperative normocalcemia or hypocalemia using the following equation:

\[ \text{Slope} = \frac{[(\text{Calcium Level 2} - \text{Calcium Level 1})/\text{Calcium Level 1}]/(\text{Time 2} - \text{Time 1})} \]

Sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) of sCa and iPTH levels, the combination of both, and the calcium slope were calculated using the following equations:

- Sensitivity = True Positive Findings/(True Positive + False Negative Findings)
- Specificity = True Negative Findings/(True Negative + False Positive Findings)
- PPV = True Positive Findings/(True Positive + False Positive Findings)
- NPV = True Negative Findings/(True Negative + False Negative Findings)

STATISTICS

Statistical analysis was performed with a commercially available statistic software package (SPSS 10.0 for Windows; SPSS

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After total thyroidectomy, sCa levels decreased from pre-operative levels in 166 patients (97.6%). Ninety patients (52.9%) showed sCa levels of less than 2.10 mmol/L (reference range, 2.10-2.60 mmol/L). By definition, transient postoperative hypoparathyroidism was seen in 41 patients (24.1%). Two patients (1.2%) developed permanent hypoparathyroidism. In patients without postoperative hypoparathyroidism, the mean (SD) postoperative sCa level on day 1 was 2.13 (0.14) (range, 1.55-2.45) mmol/L; in patients with postoperative hypoparathyroidism, 2.00 (0.13) (range, 1.69-2.30) mmol/L. This difference was statistically significant (P < .001).

Sixty of 127 patients (47.2%) without postoperative hypoparathyroidism and 35 of 43 patients (81.4%) classified as having postoperative hypoparathyroidism because of neuromuscular symptoms showed subnormal sCa levels (1.9-2.1 mmol/L) on the first postoperative day. Eight of 127 patients (6.3%) without postoperative hypoparathyroidism exhibited mild neuromuscular symptoms (paresthesia) on the first postoperative day; however, normal sCa levels were documented.

THYROID MORPHOLOGIC FEATURES AND FUNCTION

Transient postoperative hypoparathyroidism was observed in 24 patients (26.7%) with euthyroid nodular goiter, including 16 of 72 (22.2%) with a malignant thyroid tumor and 1 of 9 (11.1%) with thyrotoxicosis. The differences were not statistically significant. Permanent hypoparathyroidism developed in 1 patient with euthyroid nodular goiter and in another patient with thyrotoxicosis, whereas no patient with a malignant thyroid tumor showed this condition.

CENTRAL LYMPH NODE DISSECTION

Twenty-four of 102 patients with CND (23.5%) and 19 of 68 patients without (27.9%) developed transient postoperative hypoparathyroidism (P = .35). Fifty-seven patients (55.9%) underwent bilateral and 45 (44.1%) underwent unilateral CND. There were no significant differences for development of postoperative hypoparathyroidism between patients with unilateral or bilateral CND (P = .85) or between patients without CND or with unilateral (P = .65) or bilateral (P = .52) CND. Neither of the 2 patients with permanent hypoparathyroidism underwent CND.

PARATHYROID AUTOTRANSPLANTATION

Thirty-one of the 85 patients with parathyroid autotransplantation (36.5%) and 12 patients without (14.1%) developed transient postoperative hypoparathyroidism. This difference was statistically significant (P = .001). Both of the patients who developed permanent hypoparathyroidism underwent parathyroid autotransplantation. The number of autotransplanted parathyroid glands did not affect the rate of transient or permanent postoperative hypoparathyroidism.

Surgical Team

Nineteen of 98 patients (19.4%) undergoing operation by the advanced specialist in endocrine (thyroid) surgery (B.N.), 2 of 5 patients (40.0%) undergoing operation by an experienced general surgeon, and 22 of 67 patients (32.8%) undergoing operation by residents developed transient postoperative hypoparathyroidism. Both of the patients who developed permanent hypoparathyroidism underwent operation by residents. The differences in transient and permanent hypoparathyroidism owing to the experience of surgeon were not statistically significant.

PREDICTION OF HYPOPARATHYROIDISM

Total sCa Levels

Predicting hypoparathyroidism on the first postoperative day by measuring total sCa levels showed a sensitivity of total sCa levels of 18.6% with a specificity of 96.1%. The PPV was 61.5% and the NPV was 77.7%. On the second postoperative day, the sensitivity of sCa level measurement rose to 62.8%, with a specificity of 92.9%. The PPV for this measurement was 75.0%, with an NPV of 88.1%

The highest value of total sCa measurement to predict hypoparathyroidism was documented on the third postoperative day with a sensitivity of 72.1%, a specificity of 92.9%, a PPV of 77.5%, and an NPV of 90.8%. On the fourth postoperative day, a sensitivity of 32.6%, a specificity of 95.3%, a PPV of 76.0%, and an NPV of 83.4% were observed (Table 1).

sCa Slope

A positive sCa slope, strongly predictive of a stable postoperative sCa level, showed a sensitivity of 88.4%, a specificity of 35.4%, a PPV of 31.7%, and an NPV of 91.0% (Table 1).

iPTH Level

Twenty-two of 127 patients (17.3%) without postoperative hypoparathyroidism showed iPTH levels of less than 15 pg/mL (to convert to nanograms per liter, multiply by 0.1053) (reference range, 15-60 pg/mL) on the first postoperative day. The iPTH level of less than 15 pg/mL was observed in 4 patients as late as the fourth postoperative day. One of 41 patients (2.4%) with transient postoperative hypoparathyroidism had a normal iPTH value on the first postoperative day, and none of these patients had a normal iPTH value on the fourth day. Forty of the 41 patients (97.6%) with transient hypoparathyroidism had normal iPTH levels 4 weeks after the operation. In 1 patient, iPTH levels were in the normal range 6 months postoperatively. Mean postoperative iPTH levels are shown in the Figure.
The sensitivity of iPTH levels as the only predictive value for hypoparathyroidism on the first postoperative day (defining hypoparathyroidism with iPTH levels of 15 pg/mL or less) was 97.7%, with a specificity of 82.6%. The PPV was 65.6% and the NPV was 99.1%. The same sensitivity (97.7%) could be documented for the iPTH levels measured on the fourth postoperative day. On that day, the specificity, PPV, and NPV were 96.1%, 87.5%, and 99.1%, respectively.

Intact PTH levels of less than 15 pg/mL on the first postoperative day were more sensitive to prediction of hypoparathyroidism than iPTH levels of less than 12 or less than 10 pg/mL. The PPV and NPV could be increased to 79.0% and 95.0%, respectively (sensitivity, 88.0%; specificity, 92.0%), when hypoparathyroidism was defined as an iPTH level of 10 pg/mL or less (Table 2).

Combination of sCa and iPTH Levels

Using the combined interpretation, we observed the best result with iPTH values (definition of hypoparathyroidism, an iPTH level of ≤15 pg/mL) measured on the first postoperative day and sCa values (definition of hypoparathyroidism, sCa level of <1.9 mmol/L) measured on the second postoperative day. The combined measurement demonstrated a sensitivity of 96.3% with a specificity of 96.1%, a PPV of 86.0%, and an NPV of 99.0% (Table 2).

COMMENT

In addition to RLN palsy, clinically apparent postoperative hypoparathyroidism is a major and sometimes severe complication after total thyroidectomy.²,³,¹⁸-²¹ Controversy exists over the most relevant factors causing the development of postoperative transient or permanent hypoparathyroidism. Decreased total sCa levels measured on postoperative day 1 were observed in 97.6%. This phenomenon has frequently been debated and often partially explained by hemodilution after surgery.¹⁹,²¹ However, decreasing sCa levels within the first 3 days postoperatively may be caused by the surgical strategy used in this study, such as dissecting the RLN extensively in every patient to avoid permanent RLN palsy. Although performed by microdissection, this procedure may partially interrupt the blood supply of the parathyroid glands, leading to transient hypocalcemia. There was also no additional risk associated with CND in this patient series because no significant difference in the number of patients with and without hypocalcemia could be documented postoperatively by comparing patients with and without CND. This is in contrast to findings by others.²² Furthermore, the surgeon’s experience in thyroid surgery did not factor into development of postoperative hypocalcemia.

In a review of the literature, there are different definitions of postoperative hypoparathyroidism after thyroidectomy, mostly based on total sCa levels.⁵,¹⁷,²³-²⁵ More recently, the iPTH levels measured intraoperatively, perioperatively, or in the immediate postoperative period are recommended to classify and predict postoperative hypoparathyroidism more clearly.⁵-⁷,¹⁴ According to different definitions, the rates of developing hypoparathyroidism after thyroidectomy range from 1.6% to 50%,¹,² which seem to be high and should not occur in specialized endocrine surgical units.

In the present study, postoperative hypoparathyroidism was defined as total sCa levels of less than 1.90 mmol/L, with or without neuromuscular symptoms. Also,
patients with subnormal sCa levels and symptoms were classified as patients with hypoparathyroidism. Initial iPTH levels of less than 15 pg/mL were used for a better definition. By definition, transient hypoparathyroidism after total thyroidectomy was documented in 41 of 170 patients (24.1%). An additional 2 patients (1.2%) developed permanent hypoparathyroidism.

Controversy exists concerning the most relevant measurements and the best time for their determination in predicting postoperative transient or permanent hypoparathyroidism. Some studies describe decreasing sCa levels within the first 48 hours after surgery as a safe predictor of postoperative hypoparathyroidism. In contrast to these studies, we found that total sCa levels alone, measured during the first 2 postoperative days, cannot predict transient hypoparathyroidism correctly. Sixty of 127 patients (47.2%) without postoperative hypoparathyroidism and 35 of 43 patients (81.4%) classified as having postoperative hypoparathyroidism because of their neuromuscular symptoms demonstrated subnormal sCa levels on the first postoperative day. Eight of the 127 patients (6.3%) had mild neuromuscular symptoms (paresthesia) on the first postoperative day, although normal total sCa levels were documented. Therefore, clinical symptoms may not correlate to biochemical measurements.

Taking total sCa levels as the only measurements to predict the risk of transient or permanent postoperative hypoparathyroidism, we observed that total sCa levels of less than 1.9 mmol/L on the third postoperative day have the highest sensitivity (72.1%) and specificity (92.9%) with a PPV of 77.5% and an NPV of 90.8%. The sensitivity of sCa measurements decreased to 32.6% on the fourth postoperative day. The specificity and PPV increased from 82.6% to 96.1% and from 65.6% to 87.5%, respectively. One patient had an iPTH level of 15.2 pg/mL on the first postoperative day, which decreased to 8 pg/mL on the fourth day. Four of 127 patients (3.1%) without hypoparathyroidism had iPTH levels of less than 15 pg/mL. The sensitivity of iPTH measurements (97.7%) did not differ from the first to the fourth postoperative day. The specificity and PPV increased from 82.6% to 96.1% and from 65.6% to 87.5%, respectively.

Some authors recommend intraoperative or perioperative iPTH monitoring using a quick iPTH assay for predicting the postoperative parathyroid function. Although Lindblom et al. found no overall significant difference between measurements of intraoperative iPTH levels and measurements of sCa concentrations on the first postoperative day for predicting long-term hypoparathyroidism, monitoring of intraoperative iPTH levels could predict which patients may need intravenous calcium supplementation during the first 24 hours postoperatively. Intravenous calcium supplementation was not necessary in any of the 170 consecutive patients in this series. However, in most studies recommending intraoperative monitoring of iPTH levels, levels that were less below the normal range at the end of or immediately after the operation were highly correlated with postoperative hypoparathyroidism and seemed to allow for early prediction, with a sensitivity and specificity ranging from 71% to 100%. Monitoring of iPTH levels during thyroidectomy may be easily organized in centers of endocrine (thyroid) surgery. However, most patients with thyroid problems are treated in smaller surgical units. Therefore, monitoring of intraoperative iPTH levels may be a logistical problem and increase the costs. Measurement of iPTH levels on the first postoperative day seems more cost-effective as a reliable tool, with a sensitivity of nearly 100%, to determine patients who are at risk of developing postoperative transient or permanent hypoparathyroidism.

To avoid permanent hypoparathyroidism, autotransplantation of parathyroid glands is recommended. Zedenius et al. found that, after routinely transplanting at least 1 parathyroid gland into the sternocleidomastoid muscle, none of their 100 consecutive patients undergoing total thyroidectomy developed permanent hypoparathyroidism. A similar experience was reported by Lo and Lam. Parathyroid autotransplantation was per-
formed on demand in our series. Both patients with permanent hypoparathyroidism underwent parathyroid autotransplantation. Parathyroid autotransplantation does not provide absolute protection against permanent hypoparathyroidism.\(^7\)

In patients undergoing parathyroid autotransplantation, it is not clear whether the transplant itself, the parathyroids left in situ, or possible supernumerary glands provide sufficient parathyroid function to maintain eucalcaemia. Twenty-nine of 41 patients (70.7%) with transient postoperative hypoparathyroidism underwent transplantation of 1 gland or more, whereas 12 patients (29.3%) had no parathyroid autotransplant. The parathyroid function usually recovers within 4 weeks.\(^28\) After cessation of calcium and calcitriol supplementation therapy, all but 2 of the 43 patients with iPTH levels of less than 15 pg/mL on the first or fourth postoperative day had normal sCa and iPTH levels 4 weeks or 6 months later. Therefore, hypoparathyroidism was classified as transient in these 41 patients. Hypoparathyroidism in 2 patients with iPTH levels of less than 15 pg/mL after 6 months was classified as permanent, with the sCa levels in these patients at hypocalcemia level without calcium and calcitriol supplementation.

**CONCLUSIONS**

We compared different ranges of iPTH levels for predicting hypoparathyroidism more clearly, and the results of the study show that postoperative iPTH levels of less than 15 pg/mL on the first or fourth postoperative day are more sensitive to prediction of hypoparathyroidism than iPTH levels of less than 12 or less than 10 pg/mL.

In this series, measuring iPTH levels 24 hours after total thyroidectomy in combination with sCa levels on the second postoperative day allowed the prediction of hypoparathyroidism with a high sensitivity, specificity, and PPV. Patients with iPTH levels of 15 pg/mL or less and sCa levels of 1.9 mmol/L or less were at increased risk of developing postoperative hypoparathyroidism. Observation of sCa and iPTH levels independently showed different sensitivity and specificity on different postoperative days. Therefore, on the first 2 postoperative days, interpretation of iPTH levels in combination with sCa levels seems an optimal strategy for predicting patients at risk of hypoparathyroidism. This concept makes a safe discharge on the second day possible with minimal laboratory efforts and costs.

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