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Serum calcium relative decline as a predictor of post thyroidectomy hypocalcaemia

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Abstract

Objectives. To assess the value of corrected calcium decline at 6 hours as a predictor of hypocalcaemia post total thyroidectomy by comparing it to the currently widely used intact parathyroid hormone.

Methods. A retrospective cohort study of patients who underwent total thyroidectomy from January 2016 to February 2020. Serum intact parathyroid hormone and corrected calcium data pre-operatively and 6 hours post-operatively were obtained. Receiver operating characteristic curves were used to compare corrected calcium decline at 6 hours versus 6 hours for relative intact parathyroid hormone decline as predictors of hypocalcaemia, and the area under the curve for each metric was reported.

Results. Patients included in this analysis totalled 209. The receiver operating characteristic analysis suggested that corrected calcium decline at 6 hours has a similar predictive value to 6 hours relative intact parathyroid hormone. The areas under the curves for predicting hypocalcaemia were 0.797 for corrected calcium decline at 6 hours and 0.737 for 6 hours relative intact parathyroid hormone, but the difference (0.06) was not statistically significant.

Conclusions. Our results suggest that corrected calcium decline at 6 hours has a similar predictive value to 6 hours relative intact parathyroid hormone and hence has the potential to predict post-operative hypocalcaemia.

Introduction

Hypocalcaemia is one of the most common complications following total thyroidectomy with a reported incidence of 1.6–38 per cent. This huge variation in reported incidence is due to the significant heterogeneity in how hypocalcaemia has been evaluated. Timing of investigation collection, experience of the surgeon, different definitions of hypocalcaemia (symptomatic *vs* asymptomatic *vs* biochemical), and pre-operative and post-operative supplementation protocols all contributed to this heterogeneity.[1,2] Hypocalcaemia is usually asymptomatic, but it can present with different symptoms including paraesthesia, perioral or finger tingling and, in severe cases, can manifest with life-threatening events such as heart block.[3–6] Possible aetiologies include injury to the parathyroid gland or even accidental removal during dissection due to its proximity with the thyroid gland.

Given the rising incidence of thyroid cancers and the current context of growing health care costs, a shift towards outpatient day-case surgeries to minimise the expense associated with inpatient hospitalisation is attractive.[7] However, development of hypocalcaemia usually occurs 24–48 hours post-operatively which represents the main obstacle for early hospital discharge.[8] Intact parathyroid hormone as an early predictor of post-operative hypocalcaemia has been extensively investigated. Many algorithms have been published in the literature and although there are variations in the timing, the type of assay used, and threshold of intact parathyroid hormone (PTH), a general consensus in using the test as a predictive method exists.[3,9,10] A recent publication of the American Thyroid Association has reported that an intact PTH threshold of less than 15 pg/mL would suggest an increased risk for acute hypocalcaemia.[1]

An issue with a PTH-related algorithm is that it might not work when patients have low vitamin D levels. Low vitamin D leads to high PTH values, leading to a secondary hypoparathyroidism. A 2014 study done in India concluded that the fall in PTH after total thyroidectomy in vitamin-D-deficient patients is unreliable in predicting hypocalcaemia.[11] In Oman and many other middle eastern countries, vitamin-D deficiency is common. The 2004 Oman National Survey revealed that vitamin D_3 stores are low among healthy Omani females of childbearing age.[12] Another issue with intact PTH is the turnaround time which is not fast enough for decision-making and at times takes more than 48 hours to be reported in our institution.

To explore this point further empirically, this study has focused on evaluating the value of corrected calcium decline at 6 hours as an early predictor of hypocalcaemia post total thyroidectomy by comparing it to the currently widely used intact PTH.

Main Article

Hamed Al Maawali takes responsibility for the integrity of the content of the paper

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Materials and methods

Patient population

This is a retrospective cohort analysis that was approved by the Research Ethics Committee in Sultan Qaboos University hospital. Demographic, clinical and laboratory data were obtained from the medical records of all patients who underwent a total thyroidectomy with or without central neck dissection between 1 January 2016 to 31 January 2020, performed by a single surgeon at a university-based tertiary hospital. Patients undergoing lateral neck dissection in the same setting were excluded.

Definition and measurements

Corrected calcium levels and intact parathyroid hormone (PTH) levels were collected pre-operatively and post-operatively. Post-operatively, our institution follows a longstanding standardised protocol for the collection of calcium and PTH samples. This protocol is initiated following the conclusion of surgical procedures, specifically defined as the closure of the surgical site, including skin closure. Blood collection orders, along with their respective timestamps, are entered into our electronic system by the surgical team. These orders are then executed by nursing staff according to the specified timeline.

Post-operative hypocalcaemia was defined as a binary variable, categorised as either present or absent. It was identified by any corrected calcium level less than 2.15 mmol/L (our laboratory reference range 2.15–2.55 mmol/L) and/or the presence of symptoms such as paraesthesia in the hands, feet, or perioral region which resolved after administration of calcium supplements. The absolute corrected calcium decline was defined as: Δ corrected calcium = (pre-operative corrected calcium) – (6 hours post-operative corrected calcium). Relative corrected calcium decline was defined as: (Δ corrected calcium)/(pre-operative corrected calcium) = (pre-operative corrected calcium − 6 hours post-operative corrected calcium)/(pre-operative corrected calcium). Intact PTH was estimated by the electrochemiluminescence immunoassay method (our laboratory normal range: 1.6–6.9/L.). The absolute intact PTH decline was defined as: Δ intact PTH = pre-operative intact PTH) – (post-operative 6 h intact PTH). Relative intact PTH decline was defined as: Δ intact PTH = (pre-operative intact PTH − post-operative 6 h intact PTH)/(pre-operative intact PTH).

All patients who developed hypocalcaemia were given oral calcium and vitamin D supplements.

Statistical analysis

Data were summarised using descriptive statistics. Categorical variables were summarised using frequency and percentages. Continuous variables were summarised using mean and standard deviation. Receiver operating characteristic curves were used to compare post-operative 6 hours absolute/relative corrected calcium decline to absolute/relative intact PTH decline as predictors of hypocalcaemia, and the area under the curve for each metric was reported with a standard error (SE). A p-value of less than 0.05 was considered statistically significant. All analyses were carried out using MedCalc 25 (MedCalc Software, Ostend, Belgium).

Results and analysis

Initially, 323 patients were enrolled, but only 209 patients had complete intact PTH data. The remaining 114 patients were excluded due to missing pre-operative intact PTH as they were referred from different institutions and their pre-operative test results were not recorded in our system.

A comparative analysis of 323 patients revealed demographic disparities between those with complete and missing intact parathyroid hormone (PTH) data. Among the 209 patients with complete intact PTH data, 173 (82.8 per cent) were female and 36 (17.2 per cent) were male. In contrast, in the 114 patients with missing intact PTH data, females constituted a higher proportion, with 106 (93 per cent) female patients and 8 (7 per cent) male patients ($p < 0.011$). In addition, the mean age was significantly higher in the group with missing intact PTH data compared to the group with complete data ($t = -3.422$, $p = 0.002$). However, there was no statistical significance ($p = 0.584$) between the rate of hypocalcaemia in the complete data group (36.4 per cent) and in the missing intact PTH data group (40.4 per cent). Also, 21 patients (10 per cent) of the complete intact PTH group had central neck dissection compared to six patients (5.3 per cent) in the missing intact PTH group, but this was not statistically significant ($p = 0.206$). The comparative receiver operating characteristic analysis demonstrated non-significant differences in diagnostic test performance between the two groups, with an area under the curve of 0.797 for patients with complete intact PTH data and 0.839 for those with missing intact PTH data ($p = 0.4022$).

Out of the 209 patients included in the final analysis, corrected calcium and PTH samples were collected pre-operatively with a mean time of 11 days and a range of 1–89 days. Post-operatively, the mean collection time was 6.83 hours, with a range of 5.5–8.2 hours. Hypocalcaemia was observed in 76 patients (36.4 per cent). Receiver operating characteristic analysis was used to compare post-operative intact PTH relative decline at 6 hours, intact PTH absolute decline at 6 hours, absolute corrected calcium decline at 6 hours, and corrected calcium relative decline at 6 hours (Figure 1). This suggested that corrected calcium relative decline at 6 hours has a similar predictive value to intact PTH relative decline at 6 hours. The area under the curve for predicting hypocalcaemia were (area under the curve = 0.789, SE = 0.032 for corrected calcium absolute decline; area

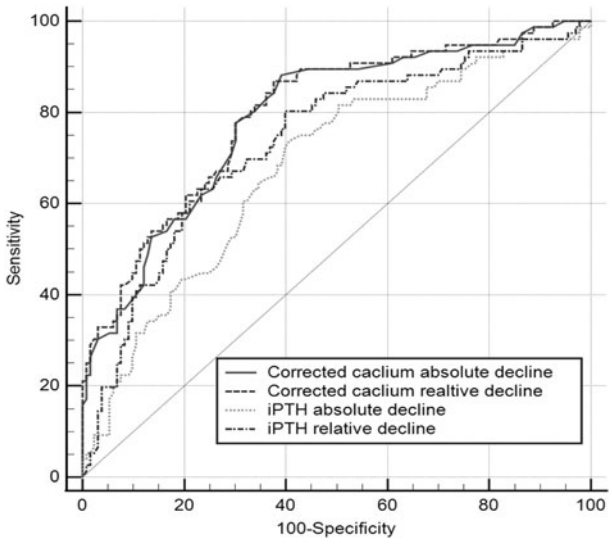

Figure 1. Receiver operating characteristic curves of post-operative corrected calcium absolute decline and relative decline at 6 hours compared with intact parathyroid hormone absolute decline and relative decline at 6 hours as predictors of post-operative hypocalcemia; iPTH = intact parathyroid hormone.

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under the curve = 0.797, SE = 0.032 for corrected calcium relative decline; area under the curve = 0.682, SE = 0.038 for intact PTH absolute decline; area under the curve = 0.737, SE = 0.036 for intact PTH relative decline).

Intact PTH relative decline was a significantly better predictor than intact PTH absolute decline (Δ area under the curve = 0.055, SE = 0.019, $p = 0.0003$). Corrected calcium relative decline and absolute decline had a larger area under the curve compared to relative intact PTH decline but the difference was not statistically significant (intact PTH relative decline *vs* corrected calcium relative decline Δ area under the curve = 0.060, SE = 0.048, $p = 0.206$, intact PTH relative decline *vs* corrected calcium absolute decline Δ area under the curve = 0.052, SE = 0.048, $p = 0.277$).

A further subgroup analysis was carried out to see the effect of central neck dissection on the diagnostic performance of the aforementioned tests. Out of the 209 patients included in the analysis, 21 underwent central neck dissection. Among these patients, 16 (76.2 per cent) did not develop hypocalcaemia, while 5 (23.8 per cent) experienced hypocalcaemia. In contrast, among the 188 patients who did not undergo central neck dissection, 117 (62.2 per cent) did not develop hypocalcaemia, and 71 (37.8 per cent) experienced hypocalcaemia. These findings suggest a potential association; however, this was not statistically significant ($p = 0.24$). Furthermore, a receiver operating characteristic analysis that was carried out after excluding patients who had central neck dissection showed similar results with calcium relative decline, having a larger area under the curve of 0.807 compared to 0.775 for intact PTH relative decline, but the difference was not statistically significant (Δ area under the curve = 0.032, SE = 0.05, $p = 0.520$).

Discussion

Hypocalcaemia following total thyroidectomy is a common complication, and given its high incidence (reaching 38 per cent) and the life-threatening events it can cause, an early predictive method is required to allow for a safe and cost-efficient early hospital discharge.[3–6,13] The purpose of this study was to evaluate the usefulness of corrected calcium decline at 6 hours as a predictor of hypocalcaemia against the currently widely used intact PTH. Our results suggest that corrected calcium decline at 6 hours has a similar predictive value to intact PTH relative decline.

The use of early post-operative calcium levels has been suggested as a way to predict the occurrence of hypocalcaemia. Marohan and LaCavita enrolled 150 patients with total/near-total thyroidectomy and followed their calcium levels for the first 24 hours. They found that serial serum calcium determinations used to construct a three-point calcium curve at 20 hours after operation can reliably and safely identify patients at risk to have clinically significant hypocalcaemia.[14] Another study by Adams *et al.*, looked into post-operative calcium slope to predict hypocalcaemia and included patients undergoing both total thyroidectomy and unilateral parathyroidectomy. They concluded that a positive slope in non-parathyroid surgeries predicted normocalcaemia in all patients.[15] Similarly Husein *et al.*, prospectively studied 68 patients undergoing total thyroidectomy and calcium slope was calculated from the 6- and 12-hour serum corrected calcium levels. Their data showed successful prediction of calcium status post total thyroidectomy using the slope of the 6- and 12-hour calcium levels.[16]

- Hypocalcaemia is the most common complication following total thyroidectomy and represents the main obstacle to early discharge from hospital
- A general consensus in using intact parathyroid hormone as a predictive method exists but an issue with intact parathyroid hormone is the turnaround time which is not fast enough for decision-making
- This study investigated the value of corrected calcium decline at 6 hours as a predictor of hypocalcaemia post total thyroidectomy by comparing it to the currently widely used intact parathyroid hormone
- Our results suggest that corrected calcium relative decline has a similar predictive value to intact parathyroid hormone decline and hence has the potential to predict post-operative hypocalcaemia

Our study methodology is different in the timing of optimal threshold for prediction, 6 hours in our analysis, compared to a range of 12–24 hours in the published studies noted above. Another difference is the definition of hypocalcaemia which is 2.14 mmol/L in our centre, and is 1.9–2 mmol/L in the other studies. We calculated the relative decline of corrected calcium while other authors used a slope where time is a factor in their analysis. Our main goal was to predict hypocalcaemia very early to allow same-day discharge while their method needed 2–3 readings of calcium up to 24 hours. No direct comparison can be made between our study and the previously published works, and no articles published in English were found, to our knowledge, looking at the absolute and relative corrected calcium decline at 6 hours.

Extensive research that has been conducted on intact PTH as an early predictor of post-operative hypocalcaemia has reached a general consensus in using the test as a predictive method.[3,7,9,10] Noordzij *et al.* conducted a systematic search and obtained 457 patients from 9 published studies and found that a single PTH threshold (65 per cent decrease compared with pre-operative level), checked 6 hours after completing thyroidectomy, had a sensitivity of 96.4 per cent and specificity of 91.4 per cent in detecting post-operative hypocalcaemia.[17] Similarly, Al Khadem *et al.* included 119 patients in a retrospective analysis looking at intact PTH and intact PTH gradient 6 hours post-operatively to obtain a threshold for diagnosis. Their results suggest that the intact PTH gradient may be more useful than the post-operative intact PTH alone in predicting risk of post-thyroidectomy hypocalcaemia.[7] The American Thyroid Association suggested a PTH value ≥15 pg/mL, measured more than 20 minutes post thyroidectomy, would prevent the need for intensive monitoring and/or supplementation of calcium in adults, and that a value of <15 pg/mL suggests an increased risk of hypocalcaemia, which might prompt precautionary supplementation with oral calcium or hospital stay for serial calcium measurements.[1]

There is significant heterogeneity in the published literature regarding intact PTH as a predictive method. This is perhaps related to the timing of intact PTH withdrawal, the laboratory assays used for intact PTH determination, and the cut-off value used to predict hypocalcaemia.[13] In our institution, intact PTH assay, on many occasions, does not have a turnaround time that is fast enough for decision-making and the assay is not available in secondary hospitals where total thyroidectomy is routinely carried out. Hence, we needed a test that had a similar predictive value to intact PTH and our results suggest a potential use of corrected calcium relative decline at 6 hours as a predictive method.

Limitations

Several limitations to our study have been identified. This is a retrospective analysis of a patient cohort, a large number of

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patients had missing data and had to be excluded from the analysis, pre-operative intact PTH and corrected calcium measurements were taken at random times (ranging from 1 day pre-operatively up to 3 months pre-operatively). In addition, possible confounding factors such as pre-operative vitamin D status, indication for surgery, and evidence of parathyroid tissue in the specimen were not studied. Future studies should address the limitations of the present study.

Conclusion

Our results suggest that corrected calcium relative decline at 6 hours has a similar predictive value to intact PTH relative decline at 6 hours and hence has the potential to predict post-operative hypocalcaemia.

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