Braz J Otorhinolaryngol. 2014;80(6):551–553

Brazilian Journal of
OTORHINOLARYNGOLOGY
www.bjorl.org

LETTER TO THE EDITOR

Perioperative parathyroid hormone measurements in thyroid surgery: one stone to hit three birds☆

Determinações do paratormônio no perioperatório em cirurgia de tireoide: como matar três coelhos de uma cajadada só

Dear Editor,

Despite the fact that post-thyroidectomy hypocalcemia is the most common procedural complication and the most common reason for prolonged post-operative hospital stay, there are still a variety of protocols used to manage this issue and continuous debate that has failed to produce a consensus or useful guidelines. Currently, surgeons are divided into two major schools: (1) routine calcium supplementation to all patients and early discharge, or (2) selective calcium supplementation for those deemed at high risk of hypocalcemia or those who develop hypocalcemia with delayed discharge in this subset.

Prophylactic supplementation to all patients

The first protocol, starting all post-thyroidectomy (not undergoing lobectomy) patients on routine calcium with or without vitamin D as a prophylactic regimen, should manage most mild transient hypocalcemia and hasten early hospital discharge. Singer et al. suggested prophylactic calcium supplementation without routine laboratory assessment.[1] A three-week taper of Os-Cal with D (a common calcium supplement, available from multiple manufacturers that contains 500 mg of calcium carbonate and 200 IU of cholecalciferol), started as 1 g of calcium three times daily in the first week, twice daily in the second week, and then once daily in the third week until discontinuation at the end of the third week. The estimated cost of this regimen was $15, and the authors reported 23 (7.5%) patients who required further treatment for hypocalcemic symptoms, two of whom requiring hospital admission and intravenous calcium supplementation. The duration of hospital study was not mentioned.

The major critics for this approach are: (1) that it is an unnecessary treatment for the majority of patients, who do not require supplemental calcium that it can be associated with adverse gastrointestinal effects, and may suppress normal parathyroid hormone secretion with prolonged suppression of gland function[2]; (2) it may delay identification of severe hypocalcemia symptoms in profoundly hypoparathyroid patients, which may put them at risk of developing severe signs and symptoms after they have left the hospital; (3) some patients may still need laboratory assessment of serum calcium and PTH levels after hospital discharge to ensure PTH function and exclude overt hypercalcemia; (4) while the cost may seem low, the cost burden of unnecessarily treating over 70% of patients and treating their side effects was not accounted for; and (5) if we accept the possible adverse effects for the benefit of possible cost saving, it may not be safe to discharge these patients before 6 h. Six hours is the common consensus for minimal post-thyroidectomy hematoma monitoring period; however, recently this 6 h duration was questioned after the finding that in 53% of patients who developed a hematoma it occurred after the first 6 h.[3] Likewise, Landry et al. found that limited supplementation to high-risk patients would eliminate unnecessary calcium and vitamin D intake and follow-up assessments in up to 58% of patients.[2]

Selective supplementation to high-risk patients

This recommendation went through different stages of development. One of the earlier approaches was to observe the slope of serial calcium levels, if the slope becomes positive (with two measurements at 6 and 12 h), then the patient will have a high chance to remain normocalcemic.[4] However, since the nadir in serum calcium may not be reached until 48 h after surgery, and the serum calcium levels do fluctuate after calcium replacement, this approach does not appear to be optimal.[5]

Few years later, a PTH measurement based protocols flourished, after the benefit of the ultra-short half-life of PTH (1–3 min)[5] was performed. However, huge discrepancies

☆ Please cite this article as: Terkawi AS, Al-Dhahri SF. Perioperative parathyroid hormone measurements in thyroid surgery: one stone to hit three birds. Braz J Otorhinolaryngol. 2014;80:551–3.

http://dx.doi.org/10.1016/j.bjorl.2014.08.015

in the literature have raised questions about how many measurements of PTH are needed? What is the best time for measurement? What would be the optimal PTH cutoff level? Is PTH based protocol is safe and effective?

Apart from the variation in the definitions used for hypocalcemia and hypoparathyroidism, most of these studies did not take into account the preoperative PTH level.[5–7] For example; do we have the same amount of parathyroid gland injury in two patients with preoperative PTH of 2 pmol/L and 6 pmol/L (both within the normal limits) if their postoperative PTH drops equally to 1.6 pmol/L? Will they have the same severity of symptoms? Will they require the same calcium/vitamin D doses?

We believe that the major cause in variation of cutoff PTH values is the variation in baseline (preoperative) PTH, which was not considered in most of the available studies. The variation in baseline PTH might be secondary to population norms, or more likely to the differences in vitamin D level and incidence of deficiency. Therefore, the use of percent of change, rather than absolute PTH values, would probably account for this variable.

We previously tested the accuracy of post-thyroidectomy calcium level and PTH level at different times postoperatively.[5] We found that PTH measurements at 6, 12, 20, 32, and 44 h have high predictive probability to detect clinical hypocalcemia; receiver operating characteristic area under the curve (AUC) were all equal to or above 0.95. While the AUC for the corrected calcium (cCa) level at different levels was: 6 h (AUC = 0.60), 12 h (AUC = 0.72), 20 h (AUC = 0.81), 32 h (AUC = 0.86), and 44 h (AUC = 0.88). Despite the fact that cCa accuracy markedly improved in the second day, it never reached accuracy of PTH measurement. Because all PTH measurements provided high accuracy, it was clinically meaningful to be able to base the clinical decision at the earliest measurement. Therefore, we suggested using a single early PTH measurement for hypocalcemia prediction and then use cCa for doses adjustment.

Le et al.[8] evaluated the validity and safety of single 1-h PTH for predicting hypocalcemia, and they concluded that it was very reliable and safe. Two patients in the low risk group ($n = 94$) became hypocalcemic, resulting in a negative predictive value of 98%.

The remaining criticism for the use of PTH measurement is its cost. In many hospitals, this test may be unavailable or take hours to have results. While we have experienced delay in receiving results of PTH, a new protocol allows for results within 1 h. Our laboratory has estimated the cost of a single PTH measurement at US$ 2.60; however, this number may be higher in other centers.

New insight and future directions

We recently published two articles that introduced two potential benefits from early perioperative PTH measurements by considering the amount of PTH change from preoperative (baseline) to postoperative (at 1 h).

In our first article,[9] we identified the percent change in perioperative PTH (postoperative ''at 1 h − preoperative/preoperative × 100) as a significant predictor for hypocalcemia and requirement for post-thyroidectomy calcium and vitamin D doses. Perioperative percent change in PTH (as a key factor), patient's body mass index (BMI), thyroid function status, and vitamin D status were used in models to predict required calcium and vitamin D doses. The models deliver three potential outputs (no calcium required, calcium up to 3 g per day, calcium more than 3 g per day) in the calcium prediction model, and three potential outputs (no vitamin D required, vitamin D 0.5 mcg per day, more than 0.5 mcg per day) in the vitamin D model. These outputs can help in identifying those patients who will not require either calcium or vitamin D, thus allowing for early post surgical discharge. At the same time, it allows for identification of those who require calcium with or without vitamin D and further guides their early management. Therefore, our model should allow for early discharge, avoiding unnecessary supplementation, and guide early effective management.

In our second article,[10] we also applied the concept of perioperative PTH percent change, this time to predict the prognosis and outcome of post-thyroidectomy hypoparathyroidism. The perioperative PTH percent change (as a key factor), the patient's BMI, gender, and diabetes mellitus status were used in two models. One model predicted the likelihood of PTH recovery, while the second model predicted the time for recovery. These findings should guide the treating physician in predicting the course of PTH recovery for each individual patient, which in turn should be reflected in better treatment planning and patient satisfaction.

These models have potential limitations: (1) they currently lack external validation, (2) they may not be ''user friendly'', and (3) their output has not yet been shown to be clinically meaningful. In order to further develop these models to more precisely predict the required calcium, vitamin D doses, and time to recovery, a validation sample including hundreds of hypocalcemic/hypoparathyroid patients will require multi-center collaboration. Finally, to overcome the issue of user-friendliness, these models can be translated into a smartphone software to be used by the treating physician.

In conclusion, with our findings, perioperative PTH measurements can assist the treating physician regarding three important issues (our three birds): (1) which patient is not at risk of hypocalcemia and can be discharged without ''unnecessary'' supplemental calcium and vitamin D, (2) what is the best starting dose for calcium and vitamin D for those at risk; this information should shorten the time required to control these patients' symptoms and serum Ca level; and (3) whether and when a given patient has a chance for PTH recovery? Our newly introduced methods shed a light on potentially useful approaches to the perioperative PTH. Although these methods are still immature for wide clinical implementation and need further development, we hope they will make those who recommend prophylactic supplementation revisit their theory, and weigh the numerous advantages of perioperative PTH measurements against the cost and side effects of empirical prophylactic supplementation.

Conflicts of interest

The authors declare no conflicts of interest.

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