REVIEW ARTICLE

Hypocalcemia after Thyroidectomy: The Need for Improved Definitions

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ABSTRACT

Introduction: Hypocalcemia and permanent hypoparathyroidism are important outcome measures after total thyroidectomy. The aim of this article is to identify and highlight the wide variation in the adequacy/definition of these complications as reported in the surgical literature.

Methods: Nineteen journal articles (2008) on complications of thyroidectomy and 17 journal articles (2002) on 'prediction' of post-thyroidectomy hypocalcemia derived from a PubMed search were reviewed.

Results: Only 21% of studies of describing outcome and complications of thyroidectomy defined hypocalcemia, temporary/permanent hypoparathyroidism. 47% of studies on the early prediction of hypocalcemia failed to quote their normal range of serum calcium. When stated, the biochemical definition of hypocalcemia varied from 1.8 to 2.12 mmol/l. There is no consistent definition of post-thyroidectomy hypoparathyroidism.

Conclusion: There is no consensus apparent on literature review as to what constitutes post-thyroidectomy hypocalcemia and hypoparathyroidism. The need to benchmark and define appropriate outcome measures of thyroid surgery demands that this deficit is addressed.

KEYWORDS: Thyroidectomy, complications, hypocalcemia, definition.

INTRODUCTION

Hypocalcemia after total thyroidectomy is reported to occur in 0.33 to 65% of patients.[1] Out with variations in surgical expertise and the exact nature of the procedure, this wide disparity can be further explained by the variety of laboratory ranges for normocalcemia and the lack of a widespread and consistent definition of hypocalcemia.

In addition to risks to the patient, reasons for the surgeon to take interest in calcium status after thyroidectomy include:

- Parathyroid insufficiency is a recognized outcome measure that impacts on length of stay.
- The prediction of hypocalcemia in the early post-operative phase.

The rationale for early identification of those patients at risk of postoperative hypoparathyroidism is explained by understanding that the nadir of calcium decline and the onset of symptoms do not occur until 24 to 48 hours after thyroidectomy. Patients at risk may be required to remain in hospital, require repeated blood tests or be commenced on routine calcium supplements. If one could identify within hours of thyroidectomy, the high-risk and low-risk patients, earlier management decisions could be made regarding calcium supplementation and discharge.

If studies of prediction of post-thyroidectomy hypocalcemia use different definitions for hypocalcemia, different assays for the determination of calcium and PTH levels, and different perioperative time intervals for calcium and PTH sampling, the evaluation of patients with postoperative hypocalcemia remains a challenge.

The aim of this literature review is to confirm and highlight: (1) the clear lack of a standardised definition for postoperative hypocalcemia after total thyroidectomy (2) the lack of standardized definitions for hypocalcemia in studies investigating techniques for the prediction of post-thyroidectomy hypocalcemia.

METHODS

A PubMed literature search was performed using the keywords "total thyroidectomy" and "complications." English-language articles published since 2008 were reviewed, excluding studies in which patients with thyroid malignancy, reoperation, neck dissection, parathyroid autotransplantation, pediatric patients could not be separated from those who had undergone total thyroidectomy alone. Case reports, review articles and meta-analyses were also excluded. A total of 19 studies were reviewed.

To review definitions and protocols in studies predicting postoperative hypocalcemia a PubMed literature search was performed using the key words "total thyroidectomy," "hypocalcemia," and "measurements." Case reports, review articles and studies that pooled data from other trials were excluded. A total of 17 articles published since 2002 were reviewed.

RESULTS

Post-thyroidectomy Hypocalcemia

Of the 19 articles reviewed the reported rate of transient hypoparathyroidism ranged from 5 to 71%. The rate of permanent hypoparathyroidism ranges from 0 to 3.5%.

Hypocalcemia Definitions

Sixty-three percent of the articles defined hypocalcemia, 26% defined transient hypoparathyroidism and 47% defined permanent hypoparathyroidism (Table 1). Only 4 of the 19 publications (21%) provided definitions for all three terms when reporting post-thyroidectomy complications. Five publications (26%) failed to provide any definition at all.[2-6]

In the studies that defined hypocalcemia, 58% based the definition on biochemical parameters alone.[7-13] Forty-eight percent combined both biochemical parameters and clinical symptoms.[14-18]

Variables included a failure to quote the normal range for calcium values and the use of total, corrected calcium or ionized calcium. The biochemical definitions of 'hypocalcemia' (mmol/L) included: < 1.8,[13,17] < 1.875,[14] < 1.9,[18] < 2,[7-9,11,16] < 2.05,[15] < 2.1.[12]

Definitions of transient hypoparathyroidism included: postoperative hypocalcemia that resolved in < 6 months,[8,12,18] requirement for calcium/vitamin D supplementation complete resolution occurred within 6 months,[19] need for calcium/vitamin D supplementation < 12 months.[17]

Definitions of permanent hypoparathyroidism included: hypocalcemia…6 months after surgery,[12,20] no evidence of recovery within 6 months,[9] calcium < 2.125 mm/l without calcium supplements at one year,[14] ongoing requirement for supplements[19]/vitamin D and calcium[8]/calcium ± vitamin D[16] beyond 6 months, calcium supplements at 12 months.[17]

Table 1: Journal articles that did not define hypocalcaemia and defined transient/permanent hypoparathyroidism when reporting complications of thyroidectomy

	References
No definition of hypocalcemia	2-6, 19, 20
Defined transient hypoparathyroidism	8, 12, 17-19
Defined permanent hypoparathyroidism	8, 9, 12, 14, 16-20

Prediction of Post-thyroidectomy Hypocalcemia

Hypocalcemia Definitions

A 'definition' of hypocalcemia appeared in all studies. One study defined hypocalcemia by symptoms and signs (unstated) alone,[21] 50% studies used the calcium level alone,[18,22-28] the remainder used a combination of biochemical and/or clinical criteria.[29-36]

Variables included a failure to quote the normal range for calcium values (47%) and the use of total, corrected or ionized calcium (Table 2). The biochemical definitions of hypocalcemia (mmol/L) included: Ionised calcium values < 0.95,[35] < 1,[33] < 1.17,[29] corrected or total calcium values < 1.8,[35] < 1.9,[18,28,32] < 2,[24-27,30,31,34] < 2.12.[22,23]

Table 2: Calcium assay variables in prediction of post thyroidectomy hypocalcemia

Calcium measurements	*References*
Total calcium	23, 26, 27, 30-32, 34
Corrected calcium	18, 22, 24, 25, 28, 35
Ionized calcium	29, 33, 35, 36
Reference range not provided	24, 25, 27, 28, 31, 32, 35, 36

DISCUSSION

The development of post-thyroidectomy hypocalcemia is multifactorial. The suggested contributory factors include hemodilution secondary to intravenous fluid administration during the perioperative phase, increased urinary calcium excretion secondary to surgical stress, calcitonin release after thyroid gland manipulation, and hungry bone syndrome in patients with metabolic bone disease. However, hypoparathyroidism through direct injury, removal or devascularization of parathyroid glands is the most likely cause of postoperative hypocalcemia.

The British Association of Endocrine and Thyroid Surgeons (BAETS) 3rd National Audit (http://baes.info/Pages/audit.php) reports that 30% of patients after total thyroidectomy have temporary hypocalcemia, and approximately 7% of patients are taking long-term calcium/vitamin D supplements. A multicenter audit of thyroid surgery from Sweden revealed that 7.8% of patients were treated with oral calcium supplements at their first follow up visit[37]. However, as demonstrated by Mehanna[1], using

different definitions for post-thyroidectomy hypocalcemia identified from literature review, hypocalcemia rates vary from 0 to 46% in the same cohort of post-thyroidectomy patients.

In the UK a thyroid cancer dataset is pending approval from the NHS Information Standards Board (www.ic.nhs.uk/services/datasets/dataset-list/cancer). Hypocalcemia and voice change are two proposed post-thyroidectomy complications core data items. The primary purpose of national datasets is to "enable the same standard of information to be generated from care records, independent of the organization or system that captures the base data." The development of a national dataset will allow audit of national outcomes and provide the potential for prospective assessment of different treatment modalities.

This literature review confirms that even today there is no consistent use of, rationale for, or seeming need to declare definitions of 'clinical' or 'biochemical' hypocalcemia when reporting outcomes of total thyroidectomy. The terms temporary and permanent hypoparathyroidism are equally inconsistently defined. The current interest in the early identification of patients at risk of postoperative hypocalcemia has led to a wide variety of proposed techniques measuring calcium and/or PTH soon after surgery. Comparison of results from these studies is hampered by similar imprecision.

The lack of standardized definitions for hypocalcemia, transient and permanent hypoparathyroidism after thyroid surgery precludes meaningful quantitative evaluation of different treatment options, diagnostic tests, and identification of areas for improvement. How can we take this forward?

As a first step, minimum standards should be established for reporting post-thyroidectomy hypocalcemia. These should include clear numerical definitions, whether total, corrected or ionized serum calcium was measured, and the normal reference range. If clinical signs and symptoms are used, they should be specified. In defining transient and permanent hypoparathyroidism, the temporal cut-off point should be set out and the use and details of calcium and vitamin D supplementation treatment clearly listed. The responsibility to enforce these necessary changes lies not only with the authors of submitted articles but, the reviewers and editors of the respective journals.

The implementation of such measures would not solve the difficulty in making meaningful comparisons between different studies. The second step would be for national or international specialist associations to provide their members with more stringent definitions. Given that national data collection is increasingly on the horizon, this need will be with us sooner rather than later.

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