

Role of pre and post-operative oral calcium and vitamin D supplements in prevention of hypocalcemia after total thyroidectomy

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SUMMARY: Role of pre and post-operative oral calcium and vitamin D supplements in prevention of hypocalcemia after total thyroidectomy.

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Aim. to evaluate the role of pre and post-operative oral calcium and vitamin D supplements in prevention of hypocalcemia after total thyroidectomy.

Patients and methods. 50 consecutive patients, undergoing total thyroidectomy, were enrolled. Oral calcium and vitamin D were administered in the pre and post-operative time. The data concerning symptomatic and laboratoristic hypocalcemia were collected.

Results. Incidence of symptomatic hypocalcemia was very low (6%); incidence of laboratoristic hypocalcemia was 10%. No permanent hypocalcemia developed.

Conclusions. Implementing oral calcium and vitamin D both before and after total thyroidectomy can reduce the incidence of hypocalcemia related to surgery.

KEY WORDS: Thyroidectomy - Hypocalcemia - Calcium.

Introduction

Postoperative hypocalcemia is observed in up to one third of total or completion thyroidectomy patients, being the most common complication, due to parathyroid gland insufficiency (1,2). Surgical technique has evolved to preserve parathyroid function; however, transient hypoparathyroidism still occurs owing to parathyroid manipulation, devascularization, venous engorgement or inadvertent removal of the parathyroid glands with the thyroid specimen. Hypocalcemia after total thyroidectomy (TT) is usually transient, and the incidence of permanent hypoparathyroidism is 3% or less, according to the experience of most of the endocrine surgical Units (1). Despite being self-limiting in most patients, symptomatic hypocalcemia is of particular concern because of a delay in its manifestation and the consequent need for prolonged patient hospitali-

zation or readmission. Following TT, patients are closely observed for bleeding in the first 24 h. The main discharge-limiting factor thereafter is the development of hypocalcaemia, as patients not at risk of hypocalcaemia, may be discharged on day 1 following surgery. Several authors have attempted to identify risk factors in the development of hypocalcemia. Postoperative declines in serum calcium (3,4) or parathyroid hormone (iPTH) levels (5-6) have been suggested as being reliable predictors of postoperative hypocalcemia, both in thyroid or parathyroid surgery. Although measurements of serum calcium or iPTH allow the identification of patients who have no risk of hypocalcemia after TT, the selection of patients who can be discharged early, or those requiring close monitoring of serum calcium levels or those that should receive calcium and vitamin D supplements may be very difficult. Implementation of protocols using postoperative PTH measurement has been shown to facilitate day 1 discharge after thyroidectomy (7). However, in many hospitals, rapid PTH measurement is not readily available. Routine oral calcium and vitamin D supplements have been proposed to prevent the development of symptomatic hypocalcemia and to increase the likelihood of early hospital discharge after bilateral thyroid or parathyroid surgi-

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cal procedures (8). However, since symptomatic hypocalcemia usually develops as late as 24 hours to several days after surgery, also a preoperative implementation with oral calcium and vitamin D may be a useful approach to avoid the risk of postoperative hypocalcemia. This approach may, in turn, reduce the costs associated with multiple blood samplings monitoring the calcium levels as well as the costs associated with prolonged hospitalization (8-10). Aim of our study was to evaluate the clinical usefulness of pre-operative and post-operative oral calcium and vitamin D supplements for the prevention of hypocalcemia after TT.

Patients and methods

In this prospective study, 50 consecutive patients [11 men (22%, mean age 45 ± 14.5 years) and 39 women (78%, mean age 39 ± 16 years)], undergoing TT between march 2012 and july 2012, were enrolled in collaboration with a tertiary endocrine Unit. All of the patients had no history of prior thyroid or neck surgery. Patients requiring unilateral lobectomy or subtotal or completion thyroidectomy were excluded, and only patients undergoing TT were enrolled. All patients had normal renal function at the time of surgery. Indications for surgery are listed in Table 1. Each subject provided a specific informed consent, before being part of the study. Ethical Committee of Second University of Naples approved the study protocol. The TT procedure consists of a 3- to 5-cm skin incision 1 to 1.5 cm above the sternal notch. After division of the platysma, the cervical linea alba is opened without division of the strap muscles. The thyroid lobe is dissected progressively from the strap muscles. After identification of the recurrent laryngeal nerves and parathyroid glands, the vascular pedicles of the thyroid lobe are sectioned and the thyroid lobe is removed (11-13). After hemostasis, a drain is placed in the thyroid bed. The cervical linea alba and platysma are sutured with absorbable sutures, and the skin is closed by an intracutaneous running suture. Patients were asked to take oral calcium 2g/d (1g every 12 hours)

TABLE 1 - DEMOGRAPHIC BASELINE AND PREOPERATIVE DIAGNOSIS.

	TOTAL N= 50
Sex ratio male/female	11/39
Mean age	45 ± 14.5
Multinodular goiter	42 (84%)
Carcinoma	5 (10%)
Basedow	3 (6%)

and vitamin D 880U.I/d (every 24 hours) for three days before surgery. The treatment continued from operation night to post-operative day 14. If significant hypocalcemia persisted after surgery, despite oral supplementation, intravenous calcium gluconate was administered. The medical and nursing notes were carefully examined for documentation of symptoms of hypocalcaemia. The time of administration of calcium, vitamin D analogues and intravenous fluids, in relation to serum calcium and hypocalcaemic symptoms was also noted. Serum calcium, albumin, and creatinine were measured preoperatively, on the evening of surgery ('day 0'), on the morning of day 1 and then every 24 hours until patient discharge. Total calcium concentrations were corrected for changes in serum albumin. All patients were seen in the outpatient department, 2 weeks after surgery. The reported symptoms of hypocalcaemia and the treatment required to control these symptoms were noted. Serum creatinine, albumin and calcium were measured using automated assays. The reference ranges for serum calcium were 8.5 to 10.5 mg/dL. Postoperative hypocalcemia was defined as either symptomatic or laboratory. Hypocalcemic symptoms and signs, from perioral tingling and numbness to carpopedal spasms and tetany, were registered in detail. Laboratory hypocalcemia was defined as serum total calcium concentrations of <8.0 mg/dL, even if recorded only in a single measurement.

According to our protocol previously reported (14), patients were treated with antibiotic prophylaxis with Unasyn (sulbactam/ampicillin) 1 fl (3 gr.) 30 min before surgery.

Results

All patients respected the oral supplement protocol. The thyroid diseases of the patients included multinodular goiter in 42 patients, well-differentiated thyroid carcinoma in 5, and Basedow's in 3. The operative procedures were all total thyroidectomy. No major complication occurred (e.g. laryngeal nerve paralysis, bleeding requiring reintervention). Symptomatic hypocalcemia developed only in 3 patients (6%), whereas laboratory hypocalcemia developed in 5 patients (10%). Hypocalcemic symptoms were minimal in 2 patients. Intravenous calcium was administered only to 1 patient affected by severe hypocalcemic symptoms (Table 2). Regarding this latter case, a patient affected by carcinoma, parathyroid tissue was observed on definitive histopathological analysis. Also, in two of three cases of symptomatic hypocalcemia a carcinoma was present, making surgical dissection more difficult. Permanent hypocalcemia developed in none of patients. Hypercalcemia or other side effects did not develop in

TABLE 2 - CHARACTERISTICS OF PATIENTS DEVELOPING HYPOCALCEMIA.

Hypocalcemia	Total pz (50)	Para thyroid tissue on specimen	Cancer
Absent	41 (82%)	0 (0%)	2 (4.8%)
Laboratory Hypocalcemia	5 (10%)	0 (0%)	0 (0%)
Symptomatic Hypocalcemia	3 (6%)	0 (0%)	2 (66.6%)
Requiring i.v. Calcium	1 (2%)	1 (100%)	1 (100%)

any of the patients receiving routine oral supplements.

Discussion

Postoperative hypocalcemia is a common complication following thyroidectomy. Decreased serum calcium, secondary to hypoparathyroidism, may present clinically with muscle cramps, perioral and peripheral paresthesias, carpopedal spasm or tetany, and/or confusion. In a recent study conducted on 119.517 thyroidectomy, Baldassare and colleagues found that the incidence of hypocalcemia after all categories of thyroidectomy was 5.5% (10). Also, hypocalcemia occurred significantly more often after total thyroidectomy than after unilateral thyroid lobectomy. Patients treated by thyroidectomy with concomitant neck dissection were more likely to develop hypocalcemia than patients who underwent only total thyroidectomy.

TT is the preferred option in the treatment of most thyroid surgical pathologies, especially in thyroid cancer, in which the routinely use of FNAB has allowed in the last decade a precocious diagnosis (15-19), and Grave's disease complicated by ophthalmopathy (20,21). Nevertheless, in these patients, due to potential infiltrative patterns, lymph node metastases or consensual inflammatory adhesences temporary and definitive hypoparathyroidism rates results more elevated similar to the evidence of prognosis for cancer disease as observed in our experience (22-26).

Our study shows that combination of pre and post-operative oral calcium and vitamin D supplements can reduce the incidence of hypocalcemia after TT. In fact, this treatment avoided significant decrease of serum calcium levels. The observed patients referred a minimal symptomatology and intravenous calcium administration, for persistent significant hypocalcemia, resistant to oral calcium and vitamin D therapy, was required only in one case. However, the hypocalcemic status was due to the accidental removal of parathyroid tissue, as confirmed by hystological analysis. The implementation of oral calcium and vitamin D is not new. However, this protocol is usually applied only in the sudden post-operative period. The role of routine cal-

cium supplements in the prevention of hypocalcemia after thyroidectomy was evaluated in two recent studies. Moore reported that only 4 of 124 patients, who received daily treatment of calcium (5 g) after bilateral thyroid resection, developed hypocalcemia, and 1 required administration of intravenous calcium. Based on empirical observations, the prophylactic use of oral calcium to reduce the risk of hypocalcemic crisis and increase the likelihood of early hospital discharge was recommended (9). In a prospective control study, Bellantone reported that only 3 of 26 patients (11%) receiving oral calcium supplement (3 g/d) had symptoms related to hypocalcemia after total thyroidectomy, ir-respective of 11 of 27 patients (40%), not receiving calcium supplement (9). These studies suggest that post thyroidectomy hypocalcemia can be considerably prevented by the routine administration of calcium supplements. In previous studies, regimens of oral calcium alone and of a calcium and vitamin D combination, were effective. Bellantone also demonstrated that the addition of vitamin D to oral calcium supplements was associated with significantly higher serum calcium concentrations on post-operative days 2 and 3, with a lower incidence of hypocalcemia (9). Although it has been reported that vitamin D administration inhibits iPTH secretion by normally functioning parathyroid glands, prior studies and our own results showed that iPTH secretion was not affected by vitamin D administration in post thyroidectomy patients (27). Therefore, the early use of vitamin D in addition to calcium supplements can be recommended for patients undergoing TT. The dosages and duration of calcium and vitamin D administration are also of concern. Roh and Park demonstrated that routine oral calcium and vitamin D supplements were effective in reducing the incidence and severity of hypocalcemia after TT (28). Only a minority of patients, receiving the supplements, presented minimal symptoms related to hypocalcemia and higher levels of serum calcium during the first few days after TT were measured. Post-operative hypocalcemia can be reduced when a precise surgical dissection is performed, and the use of harmonic scalpel, avoiding energy spread, blood loss and edema, may reduce parathyroid function impairment (10,12,13). The drive towards a shorter hospital stay following TT has led to

evaluating the use of biochemical markers to predict the development of hypocalcaemia. Thyroid surgery may cause postoperative parathyroid insufficiency and subsequent hypocalcaemia (27). Serum level calcium assay following thyroidectomy has been used in an attempt to predict the development of hypocalcaemia. However, the measurement of total serum calcium is inaccurate, at least or in part, owing to postoperative haemodilution (28, 29). The value of PTH in predicting post-thyroidectomy hypocalcemia has been extensively investigated (30-33). Although postoperative iPTH evaluation may allow shorter hospital admission, rapid access to results of postoperative PTH measurement is not widely available in many hospitals. In addition, there is no consensus on the threshold for iPTH and the optimal timing for its measurement after thyroidectomy (34). The iPTH measurement on the first postoperative day has been shown to be a useful method to predict post-thyroidectomy hypocalcemia (35). 1–6 h after thyroidectomy iPTH serum level assay concentration, has demonstrated a higher accuracy in predicting hypocalcaemia, nevertheless it appeared to lack the de-

sirable 100% accuracy rate (20,35). In absence of preoperative data, we were not able to analyse postoperative decline in PTH. However, both absolute and relative decline have been used to predict hypocalcaemia with similar accuracy and, although similar, levels vary between institutions (34,36,37). The prevention of significant symptomatic hypocalcemia will allow early discharge of patients.

Conclusion

Our data suggest that the pre and post-operative oral calcium and vitamin D supplements may prevent postoperative hypocalcemia, allowing a safe and early discharge. This will ultimately lead to improved patient satisfaction and significant cost savings. However, this issue should be investigated by prospective, randomized, carefully designed studies including a comparison between patients receiving or not medical treatment, to better identify the role of oral supplement.

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