ORIGINAL ARTICLE

Hypocalcaemia After Total Thyroidectomy: Incidence, Control and Treatment

Jesús Herranz González-Botas,* Diana Lourido Piedrahita

Servicio de Otorrinolaringología, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain

Received 6 July 2012; accepted 12 September 2012

KEYWORDS
Hypocalcaemia; Thyroidectomy; Graves–Basedow

Abstract
Introduction: Hypocalcaemia, although usually transitory, is the most frequent complication after total thyroidectomy.
Objective: To identify factors associated with a higher risk of hypoparathyroidism and related to aetiology and surgical procedure.
Materials and methods: A total of 254 total thyroidectomies were analysed for the incidence of transitory or permanent hypocalcaemia based on the relationship with etiological and surgical factors.
Results: Transient hypocalcaemia was present in 29.1% of the cases and permanent hypocalcaemia was present in 4.7%. Postoperative hypocalcaemia was lower in patients with completion thyroidectomy than in patients that underwent total thyroidectomy in a single operation, 12% vs 31%. Patients with Graves–Basedow disease developed postoperative hypocalcaemia in 50% of the cases. Mean recovery time of parathyroid function was 5.2 months, with 72.2% of the patients recovering before 6 months.
Conclusions: Postoperative hypocalcaemia is a frequent complication of total thyroidectomy, but it is seldom permanent. Patients with Graves–Basedow disease have a higher incidence of postoperative hypocalcaemia and need closer follow-up. Postoperative calcium level analysis at 24 and 48 h after surgery is not useful for rapid identification of patients at high risk of hypocalcaemia.
© 2012 Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE
Hipocalcemia; Tiroidectomía; Graves-Basedow

Hypocalcemia postiroidectomía total: incidencia, control y tratamiento

Resumen
Introducción: La hipocalcemia es la complicación más frecuente de la tiroidectomía total, si bien pasajera en la mayoría de los casos.
Objetivo: Identificar factores patológicos y quirúrgicos, que pudieran estar asociados a un mayor riesgo de hipocalcemia.


* Corresponding author.
E-mail address: jesus.herranz.gonzalez.botas@sergas.es (J. Herranz González-Botas).

2173-5735/$ - see front matter © 2012 Elsevier España, S.L. All rights reserved.
Introduction

Postoperative hypocalcaemia is the most common complication of total thyroidectomy. Its incidence varies between 30% and 60% due to the different criteria used to define it.1-3 It is not always associated with accompanying symptoms, and in most cases it is resolved in less than 6 months. Multiple factors have been associated with an increased risk of hypocalcaemia, and there are several procedures aimed at quickly identifying which patients may develop hypocalcaemia secondary to treatment.4,5,6 Rapid identification aims to prevent the resulting clinical symptoms and reduce hospital stay, allowing a faster return of patients to normal activity, as well as a reduction in the cost of the process.

The factors associated with an increased risk of postoperative hypocalcaemia include those related to gender, type of intervention, base condition, identification of the parathyroids and/or manipulation thereof.1,6-11

The aim of this retrospective, observational study was to determine the incidence of hypocalcaemia secondary to total thyroidectomy, both primary and secondary, analysing its relationship with surgical technique and aetiological factors which may predict an increased risk, as well as to assess the usefulness of analytical methods employed for the early detection of postoperative hypocalcaemia and evaluate the treatment protocol.

Materials and Methods

We analysed total thyroidectomies, both primary and secondary (completed thyroidectomies in patients who had previously undergone hemithyroidectomy), conducted between January 2006 and June 2011. All patients underwent determination of serum calcium 24 and 48 h after surgery. Corrected calciaemia was calculated in relation to plasma proteins according to the formula: corrected Ca=measured Ca/(proteins/16)+0.55. Postoperative hypocalcaemia was considered when the level of corrected calcium was below 8 mg/dL, regardless of the presence of accompanying symptoms.

During surgery we noted identification and localisation of the parathyroids, as well as the pathology and type of surgery. Postoperative replacement therapy was begun upon the observation of clinical symptoms of hypocalcaemia (numbness, positive Trousseau) or corrected calcium levels below 7.5 mg/dL. The initial treatment in cases of positive symptoms and corrected calcium <8.0 mg/dL was administration of 20 cc of 10% calcium gluconate in a serum of 100 cc passed in 20 min. Simultaneously, we started treatment with oral calcium at a dose of 1 g every 8 h. We administered calcitriol in those cases in which the corrected calcium figures were below 7.5 mg/dL. We considered as permanent hypocalcaemia the need to maintain oral calcium supplementation, with or without calcitriol, for more than 12 months after surgery.

The quantitative variables were expressed as mean±standard deviation and the qualitative variables were expressed as absolute values and percentages with the estimation of 95% CI. In order to compare means we used the Student t test or the Mann–Whitney U test, as appropriate, after checking the normality of quantitative variables with the Kolmogorov–Smirnov test. The association between qualitative variables was estimated using the chi-square test.

Results

We analysed a total of 254 total thyroidectomies, of which 90.2% (229/254) were performed in 1 time and 9.8% (25/254) were performed in 2 procedures. A total of 83.5% (212/254) patients were female and the mean age was 51.2±15.2 years.

The rate of postoperative hypocalcaemia was 29.1% (74/254) and that of permanent hypocalcaemia was 4.7% (12/254). The mean calcium value at 24 h was 8.3±0.3 mg/dL and 8.7±0.4 mg/dL in patients without hypocalcaemia. Among patients with hypocalcaemia, the mean value at 24 h was 7.5±0.4 mg/dL and 7.7±0.8 mg/dL. The mean recovery time of hypocalcaemia was 5.2±3.7 months, with 72.2% of patients recovering before 6 months.

The incidence of postoperative hypocalcaemia was significantly higher ( P<0.05) among thyroidectomies performed...
in 1 time (31% [71/229]), than among patients intervened for completion of thyroidectomy (12% [3/25]). None of the patients treated secondarily to complete thyroidectomy developed permanent hypocalcaemia.

The incidence of permanent hypocalcaemia presented an inverse relationship with the number of parathyroids identified during surgery, although the difference was not statistically significant (Table 1). This relationship was not found when associating the number of parathyroids identified with the rate of postoperative hypocalcaemia.

The highest incidence of postoperative hypocalcaemia was found among patients with Graves’ disease (50% [13/26]) and thyroiditis (30.8% [4/13]).

The incidence of permanent hypocalcaemia was similar between patients with benign involvement (6.1% [8/131]) and patients with malignant disease, all with differentiated thyroid carcinomas (5.2% [3/58]). Neither did we find significant differences in relation to goitre size or experience of the surgeon.

The mean value of corrected calcium at 24 h was 8.3 mg/dL among patients without hypocalcaemia and 7.8 mg/dL among those with permanent hypocalcaemia. The variation of corrected calcium between 24 and 48 h postoperatively showed no significant differences enabling identification of those patients who were to develop hypocalcaemia requiring treatment.

**Discussion**

Postoperative hypocalcaemia is the most common complication after total thyroidectomy, with incidences that can vary significantly depending on the criteria used to define it.\(^2,4,12\) Serum calcium levels below normal limits do not necessarily involve symptoms.\(^12\)

As in the study by Prim et al., we identified postoperative hypocalcaemia more frequently among primary total thyroidectomies than among those performed in a second surgical procedure, in order to complete total thyroidectomy in patients who presented a neoplasm on the opposite side to a previous hemithyroidectomy or due to development of hyperplasia in the non-intervened hemithyroid.\(^10\)

Since most cases of postoperative hypocalcaemia are able to recover, completing a total thyroidectomy in a second surgical procedure enables the recovery of parathyroids which were potentially affected during the first intervention. Conversely, Ginnoir et al. found no increase in the incidence of permanent hypocalcaemia among patients undergoing surgery in 2 procedures.\(^7\)

Graves’ disease is associated with a higher incidence of hypocalcaemia. Their greater vascularisation is an added difficulty for the location and preservation of the parathyroids,\(^4,13\) although not all series coincide with these findings.\(^14\) This increased incidence of postoperative hypocalcaemia among patients with Graves’ disease, especially females, may be due to the influence of thyroid hormones on calcium metabolism and bones, as they accelerate bone formation and remodelling.\(^11\) A decrease of thyroid hormones results in an alteration of the calcium balance, leading to “hungry bone” syndrome which is analytically manifested through hypocalcaemia, hypophosphatemia and hypomagnesaemia.\(^15\) The presence of recalcification tetany or “hungry bone” syndrome has been well-documented among patients with primary hypothyroidism, due to negative calcium balance after resection of pathological glands. In patients with hyperthyroidism, anti-thyroid treatment usually improves the bone involvement caused by Graves’ disease.\(^11\) Therefore, these patients are at increased risk of developing severe symptomatic hypocalcaemia under conditions of postoperative hypoparathyroidism.\(^16\) In these cases, the administration of calcium and vitamin D is recommended before and after surgery, especially when patients have vitamin D deficiency and alkaline phosphatase is elevated.\(^11,16\)

Most thyroid carcinomas, both papillary and follicular, do not affect the thyroid capsule, which would hinder the preservation of the parathyroids, with their dissection being similar to cases of multinodular goitre. Some studies have reported a higher incidence of hypocalcaemia when performing a dissection of area VI,\(^17\) or in association with more extensive\(^12\) neck dissections or review surgery.\(^8\) In our series, the incidence was similar in both benign and malignant lesions. Neither was it associated with neck dissection, although the number of cases which met these conditions was reduced.

The functional reserve of the parathyroid is extensive, since a single functioning gland is able to maintain calcium metabolism at normal values. In our study, identification of the parathyroids was not significantly associated with a lower incidence of transient or permanent hypocalcaemia. There is no consensus on the recommendation to identify the parathyroids in order to preserve them or on the minimum number of glands to be preserved,\(^9\) although some authors discourage identification due to the risk of injury inherent to parathyroid manipulation.\(^14\) In our opinion, a careful dissection of the thyroid capsule as close as possible to the thyroid parenchyma, as well as the identification of the parathyroids prior to ligation of the inferior thyroid artery.
are important, both to avoid damaging the structure and vascularisation, and to prevent inadvertent removal along with the thyroid lobe. Ligation of the terminal branches of the inferior thyroid artery as close as possible to the thyroïd parenchyma reduces the risk of parathyroid ischaemia. The superior parathyroid, which is closer to the recurrent nerve, has an increased risk of lesion compared to the inferior, usually enclosed within the fatty tissue of the inferior area of the thyroid. Identification of the glands enables an assessment of their viability at the end of the intervention. A comprehensive review of the surgical specimen enables us to identify any glands which may have been inadvertently removed. The use of surgical magnifiers and staining methods can also aid in the identification of the parathyroids, especially when they are closely adhered to the thyroid capsule, 3,18,19 or in cases in which thyroid lobes cover them. The risk of an intrathyroid gland can be of 22%, 19 although the influence of involuntary resection of a parathyroid gland does not affect postoperative calcium levels. 1 In those cases where a gland is found attached to the removed specimen or when a gland is considered unviable due to involvement of its vascularisation, the option of transplantation into the sternocleidomastoid muscle gives excellent results. 1,3,20 In order to confirm that the gland being transplanted is a parathyroid, it is usually introduced in serum; if it is indeed a parathyroid it will sink. In cases of malignant lesions, it is advisable to confirm that the gland to be transplanted is a parathyroid through an intraoperative biopsy of a fragment.

The objective in the immediate postoperative period is to identify those patients who will develop hypocalcaemia symptoms as early as possible, in order to avoid the inconvenience of the symptoms and to reduce their hospital stay. We know that most patients will undergo a postoperative reduction of their calcaemia, but we need to know whether that decline is indicative of hypocalcaemia subsidiary of treatment or not. This fact may manifest hours or days after surgery. There is no general definition of hypocalcaemia or the time during which it should be measured. Hypocalcaemia is usually considered as a calcium level below 8.0 mg/dL, but the range of normality varies between different institutions. Other centres consider hypocalcaemia in cases when patients require administration of calcium and/or vitamin D to maintain calcaemia figures within normal limits. Permanent hypocalcaemia is considered as having insufficient parathyroid hormone (PTH) levels to maintain normal calcaemia 6 months after surgery, 21 but recovery may take more than 12 months. 1,21 In our series, 4 patients needed more than 6 months to recover their thyroid function.

The total calcium value must be calculated using the corrected calcium formula (measured in mg/dL) in relation to proteins (measured in g/dL) according to the formula: corrected Ca=measured Ca/(proteins/16)+0.55, or albumin (measured in g/dL) corrected Ca=measured Ca+0.8 (4-albumin).

A review of methods for predicting the occurrence of postoperative hypocalcaemia concluded that PTH levels, minutes or hours after the surgery, were very reliable, despite not reaching 100%. An almost normal PTH level could almost rule out progressive and severe hypocalcaemia. 22 The simultaneous assessment of PTH and calcaemia 6 h after surgery would also enable an adequate selection of patients who could be discharged on the same day of surgery with minimal risk. 23 Following the evolution of calcium levels in the postoperative period is one of the recommended procedures for identifying patients at risk. The evolution of serum calcium between 6 and 24 h after surgery enables identification of patients who will suffer hypocalcaemia, and in whom the risk of permanent hypocalcaemia is highest. 4,24,25 If the calcium increase is positive between 6 and 12 h, the patient may be discharged, with or without oral calcium, 25 and given adequate information on the attitude towards the presence of symptoms. If there is no increase and the amount of calcium is between 8 and 7.5 mg/dL at 12 h, then hypocalcaemia is unlikely and the patient may be discharged with oral calcium, outpatient monitoring and adequate information on possible symptoms and their treatment. In our environment, assessments took place at 24 and 48 h, although the data were not useful for the early identification of patients at high risk of hypocalcaemia, since patients remained hospitalised for at least 48 h after surgery. At present, postoperative determinations take place at 8 and 24 h after surgery, thus favouring a faster identification of suspicious cases and a faster discharge. The new protocol is still being studied and, at present, we do not have significant results. There is no doubt that these recommendations should be adapted to the environment at each centre, as well as the characteristics of each patient.

Prophylactic administration of calcium and vitamin D for 2 weeks is also recommended for the prevention and reduction of hypocalcaemia symptoms, facilitating a faster discharge and reducing the cost per process. 26 In our environment, the mean expenditure per hospital bed was 545 €/day, whilst the cost of the calcium and protein analyses was about 0.1 € and that of the PTH analysis was 2.59 €. Treatment with calcitriol represented an expense of 0.2 €/day (0.25 mg/24 h) and with oral calcium 1.6 €/day (2 doses/8 h). This means that the daily expenditure for a patient at risk of hypocalcaemia controlled on an outpatient basis would be about 14 € weekly, including both treatment and control analyses, as opposed to 545 €/day of hospital stay if patients were admitted until their calcaemia levels became normalised. A study by Rigo et al., which analysed the costs of total thyroidectomy with a new protocol for the postoperative control of calcaemia based on perioperative PTH concentrations, was able to reduce the cost of total thyroidectomies from 3948 € to 3608 € and improve cost effectiveness from 1667 €/day of unnecessary hospitalisation to 1109 €/day of unnecessary hospitalisation. 27 Lecerf et al. recommend hospital discharge at 24 h after surgery for patients whose PTH value at 4 h presents a reduction below 68.5% compared to the preoperative level. 28

The symptoms of acute hypoparathyroidism are primarily manifested through the presence of perioral paresthesia, tingling in the hands and legs, and anxiety. Upon suspicion of hypocalcaemia we should look for the Trousseau and Chevostek signs. The first consists in the appearance of painful spasms in the hand when a pressure cuff is maintained above systolic pressure for 3 min. The Chevostek sign involves contraction of the facial musculature upon striking the facial nerve 2 cm in front of the earlobe and below the zygomatic bone. However, the symptoms do not always run in parallel to the presence of hypocalcaemia and, conversely, hypocalcaemia does not always cause the same symptoms in all patients.
Administration of oral calcium and/or vitamin D may delay the recovery of parathyroids whose function has been affected by surgical manipulation. This inactivation may become permanent if treatment is prolonged more than necessary. For this reason, replacement therapy should be adapted to the analyses and symptoms of each patient. The presence of a corrected calcaemia level between 7.5 and 8.0 mg/dL in the absence of symptoms can be controlled by analyses at 24 h, without the need for replacement therapy, provided that corrected calcaemia levels are maintained or increased, and the patient does not report symptoms. By contrast, calcaemia below 8.0 mg/dL with symptoms should be treated with calcium supplements.

The presence of hypocalcaemia symptoms, with or positive Trousseau sign, should be considered as a medical emergency. Calcium and proteins should be determined and 20 mL of 10% calcium gluconate in 5% dextrose serum should be administered in a period of 20 min. Once the presence of hypocalcaemia is confirmed by corrected calcium levels, treatment with oral calcium carbonate supplement at doses of 1–1.5 g every 24 h should be initiated. Calcium control should be performed at 4–6 h, during which time intravenous calcium intake should be maintained. If serum calcium levels remain above 7.5 mg/dL and the patient is asymptomatic, oral calcium should be continued and serum calcium should be monitored at 24 h. If calcium levels decrease below 7.0 mg/dL, the recommendation is to administer 100 mL of calcium gluconate in 900 cc of 5% dextrose serum, at a dose of 0.5–2 mg/kg/h, whilst carrying out checks every 6 h in order to maintain calcaemia at a level between 8 and 9 mg/dL. Caution should be exercised with patients undergoing treatment with cardiac glycosides or digitalis, since hypocalcaemia increases their effect. Monitoring through serial electrocardiograms is recommended.

If the symptoms are refractory or if hypomagnesaemia is detected, magnesium should be administered orally or parenterally, according to the severity. Oral calcium supplementation is recommended in cases of hypocalcaemia below 7.5 mg/dL, in addition to the use of calcitriol at doses of 0.25 μg/day and outpatient controls until the treatment is correctly adjusted. The use of calcitriol will increase blood phosphorus levels.

Conclusions

Postoperative hypocalcaemia is the most common complication arising from total thyroidectomy, although most cases tend to recover. Patients with Graves' disease have an increased risk of developing this complication due to "hungry bone" syndrome generated by postoperative hypothyroidism. Failure to identify the parathyroid glands was associated with a higher rate of permanent hypoparathyroidism, but with no significant differences.

There are different protocols for the analysis of calcium and/or PTH in the immediate postoperative period which allow identification of those patients with an increased risk of developing symptomatic hypocalcaemia and who will require replacement therapy. These protocols enable early calcium intake, thus reducing the time until patient discharge with minimal risk of symptoms.

Conflict of Interests

The authors have no conflict of interests to declare.

References