Course of Ionized Calcium After Thyroidectomy

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Abstract

Background The goal of the present study was to investigate the course of ionized calcium after thyroidectomy and to define a cut-off value that indicates symptoms of hypocalcemia.

Methods The sample included 333 patients undergoing thyroidectomy at the University Hospital of UFMG between September 2000 and December 2005. Ionized calcium was determined before and after surgery (days 1, 2, and 30) in all patients and on postoperative days 90 and 180 in those with hypocalcemia. Asymptomatic patients received no calcium replacement therapy, irrespective of calcium concentration. Patients with clinical manifestation of hypocalcemia were treated after laboratory confirmation. The presence or absence of postoperative hypocalcemia was associated with ionized calcium concentration measured on the reported days.

Results Ionized calcium declined on the first two days after surgery in all patients when compared to preoperative levels \((P = 0.000)\). Forty-seven (34.6\%) of the 136 (40.8\%) patients with postoperative hypocalcemia had symptoms. Patients with symptomatic hypocalcemia had significantly lower ionized calcium levels than those with asymptomatic hypocalcemia \((P = 0.001)\). Fourteen (4.2\%) patients progressed to definitive hypoparathyroidism by the end of 6 months.

Conclusions Measurement of ionized calcium on postoperative days 1 and 2 is sufficient for the evaluation of post-thyroidectomy hypocalcemia. Ionized calcium concentrations <1.03 mmol/l on postoperative day 1 are indicative of the presence of symptoms and the need for treatment.

Introduction

Thyroidectomy is one of the surgeries most frequently performed worldwide, and has an acceptable incidence of complications and sequelae which, however, can be uncomfortable, debilitating and, sometimes, lethal [1]. Thyroidectomy is characterized by peculiar anatomical and metabolic complications, with hypocalcemia being one of the most clinically relevant conditions. The incidence of postoperative hypocalcemia ranges from 1.3 to 83\% and the condition may go unnoticed if not investigated carefully because it is often asymptomatic [1–3]. A sudden and intensive decline in plasma calcium concentration seems to be responsible for the occurrence of symptoms of hypocalcemia, although it is not known which calcium concentration will trigger symptoms and whether the knowledge of this concentration is of clinical importance [2].

The investigation of calcium levels during the preoperative and immediate, intermediate and late postoperative periods, as well as the determination of parathormone (PTH), may permit the identification of patients with asymptomatic hypocalcemia, patients with symptomatic hypocalcemia who require calcium replacement therapy after operation, and patients who progress to definitive hypoparathyroidism.

The objective of the present study was to investigate the postoperative course of ionized calcium after thyroidectomy.
in an attempt to define the rate of asymptomatic hypocalcemia, and to determine which patients will need calcium replacement therapy and which patients will progress to definitive hypoparathyroidism. In addition, we tried to define a calcium cut-off value that would indicate the possible occurrence or absence of symptoms of hypocalcemia and, consequently, which patients would benefit from treatment with calcium carbonate before the onset of signs and symptoms of hypocalcemia.

**Patients and methods**

The patients were evaluated prospectively and included in the study after signing a free informed consent form, according to the World Health Organization guidelines for research involving human subjects. All patients with a formal surgical indication for any type of thyroidectomy were candidates for the study. Excluded were patients with incomplete preoperative records, those who did not return for the scheduled postoperative visits, and patients with preoperative hypocalcemia or hyperparathyroidism confirmed by the measurement of ionized calcium and PTH.

The following laboratory tests were considered to be specific for this study: preoperative: measurement of blood ionized calcium concentration and preoperative PTH levels in patients with ionized calcium above normal levels; postoperative: measurement of blood ionized calcium concentration at 6:00 a.m. and on postoperative days 1, 2, and 30, ionized calcium concentration 90 and 180 days after surgery in patients with postoperative hypocalcemia, and PTH 180 days after surgery in patients with persistent hypocalcemia and requiring oral calcium replacement therapy.

Asymptomatic patients were not treated during the postoperative period, irrespective of the result of serum calcium measurement. Patients with positive Trousseau’s and/or Chvostek’s signs but without other clinical signs or symptoms were classified as asymptomatic. Patients with paresthesia, muscle cramps, tetany, or weakness, were classified as symptomatic.

When the patients progressed to clinical manifestation of hypocalcemia, this event was confirmed by laboratory tests, and calcium carbonate was administered orally at a dose of 2.0 g at 6-h intervals. In cases refractory to treatment with calcium carbonate, oral vitamin D was also administered. Highly symptomatic patients whose plasma ionized calcium concentration was below 1.00 mmol/l received an intravenous calcium gluconate bolus in combination with oral calcium carbonate at the dose mentioned above until the disappearance of clinical manifestations.

The presence or absence of postoperative hypocalcemia was associated with the following variables: onset of clinical manifestations of hypocalcemia, i.e., on the first or second postoperative day; serum calcium ion concentration measured on days 1, 2, and 30 after thyroidectomy; serum ionized calcium concentration measured 90 and 180 days after operation in patients with postoperative hypocalcemia. Definitive hypoparathyroidism was evaluated by the determination of PTH 6 months after surgery in patients in whom hypocalcemia persisted.

Transient hypocalcemia was defined as the occurrence of a post-thyroidectomy decline in blood ionized calcium concentration to below-normal levels (reference value: 1.12–1.32 mmol/l) within a period of up to 6 months after surgery, which could be asymptomatic or symptomatic, requiring calcium replacement therapy. Definitive hypoparathyroidism was defined as the persistence of hypocalcemia for more than 6 months after surgery, with the patient requiring calcium replacement therapy and presenting PTH levels below the reference value (10.0–65.0 pg/ml).

The patients also were evaluated in relation to the extent of surgery and underlying disease determined by histopathology. The laboratory tests were carried out at the Laboratory of Clinical Pathology, University Hospital, Federal University of Minas Gerais (UFMG), and included ionized calcium (reference value: 1.12–1.32 mmol/l) and intact PTH (intact molecule; reference value: 10.0–65.0 pg/ml).

Data were analyzed with the Statistical Package for the Social Sciences (SPSS), version 13.0, with the level of significance set at 5% for all tests.

**Results**

The study included 333 patients who underwent thyroidectomy performed by the Head and Neck Surgery Group of the Alfa Institute of Gastroenterology (CCP-IAG), University Hospital, UFMG, between September 2000 and December 2005. Twenty-nine (8.7%) patients were males and 304 (91.3%) were females. Patient age ranged from 8 to 88 years, with a mean age of 45 ± 15 years and a median age of 46 years. The overall mean preoperative ionized calcium concentration was 1.24 ± 0.07 mmol/l.

The overall mean ionized calcium concentration on postoperative day (POD) 1 was 1.15 ± 0.11 mmol/l, and that on POD 2 was 1.16 ± 0.10 mmol/l, with the decrease on both days being significant when compared to preoperative levels (P = 0.000). Mean ionized calcium concentration on POD 1 and 2 was 1.21 ± 0.09 and 1.21 ± 0.05 mmol/l, respectively, in patients without hypocalcemia, and 1.06 ± 0.08 and 1.07 ± 0.11 mmol/l in patients with hypocalcemia (Table 1).

Among the 136 (40.8%) patients who developed postoperative hypocalcemia, 47 (34.6%) had clinical
manifestations, 37 (27.2%) on POD 1, and 10 (7.4%) on POD 2. The mean ionized calcium concentration in patients with symptomatic hypocalcemia was 1.00 ± 0.08 mmol/l on POD 1 and 1.02 ± 0.09 mmol/l on POD 2. In patients with asymptomatic hypocalcemia, the mean concentration was 1.08 ± 0.06 and 1.09 ± 0.11 mmol/l on POD 1 and 2, respectively. Comparison of mean ionized calcium concentrations showed a significant difference between patients with symptomatic and asymptomatic hypocalcemia on both POD 1 (P = 0.000) and POD 2 (P = 0.001; Tables 1, 2).

Among the patients who were normocalcemic on POD 1 (n = 197), 24 (10.9%) developed hypocalcemia on the second day, 2 (8.3%) required oral calcium replacement therapy, and none progressed to definitive hypoparathyroidism. In patients with hypocalcemia, the mean ionized calcium concentration on POD 2 was 1.07 ± 0.04 mmol/l in those without symptoms and 1.02 ± 0.10 mmol/l in those with symptoms, with no significant difference between the two groups (P = 0.149).

At the end of 6 months, symptomatic hypocalcemia persisted in 14 (4.2%) patients who were classified as having definitive hypoparathyroidism. In patients who did not develop postoperative hypocalcemia, ionized calcium returned to preoperative levels within 30 days after operation, whereas ionized calcium concentration continued to be below preoperative levels after 30 days in those who progressed to hypocalcemia, a difference that was significant.

In patients with symptomatic hypocalcemia, all of whom received oral calcium carbonate, ionized calcium concentration was 1.14 ± 0.16 mmol/l 30 days after thyroidectomy versus 1.23 ± 0.07 mmol/l before operation (P = 0.003). Patients with asymptomatic hypocalcemia presented ionized calcium levels of 1.19 ± 0.08 mmol/l at 30 days after operation versus 1.22 ± 0.06 mmol/l before thyroidectomy (P = 0.044). These values had returned to baseline (preoperative) levels at POD 90.

With respect to the extent of surgery, mean ionized calcium concentration on POD 1 and 2 were, respectively, 1.20 ± 0.08 mmol/l and 1.21 ± 0.07 mmol/l in partial thyroidectomy (PT); 1.12 ± 0.13 mmol/l and 1.12 ± 0.11 mmol/l in total thyroidectomy (TT); 1.17 ± 0.11 mmol/l and 1.15 ± 0.08 mmol/l in subtotal thyroidectomy (ST); 1.05 ± 0.11 mmol/l and 1.06 ± 0.08 mmol/l in total thyroidectomy + neck dissection (TT + ND); and 1.06 ± 0.08 mmol/l and 1.04 ± 0.08 mmol/l in reoperation. Lower calcium levels were observed when comparing PT versus TT, TT + ND, and reoperation (P = 0.000) and ST (P = 0.038); TS × TT + ND (P = 0.010).

With respect to the histological type, mean ionized calcium concentration values on POD 1 and 2 were, respectively, 1.16 ± 0.09 mmol/l and 1.17 ± 0.09 mmol/l in colloid goiter (CG); 1.10 ± 0.11 mmol/l and 1.14 ± 0.15 mmol/l in Basedow-Graves disease (BGD); 1.11 ± 0.17 mmol/l and 1.10 ± 0.14 mmol/l in papillary carcinoma (PC); 1.18 ± 0.05 mmol/l and 1.17 ± 0.03 mmol/l in follicular carcinoma (FC); 1.09 ± 0.10 mmol/l and 1.08 ± 0.10 mmol/l in medullary carcinoma (MC); 1.14 ± 0.14 mmol/l and 1.12 ± 0.12 mmol/l in thyroiditis; and 1.16 ± 0.09 mmol/l and 1.20 ± 0.07 mmol/l in follicular adenoma (FA). Lower calcium levels were observed when comparing CG versus PC (P = 0.001), MC

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**Table 1** Ionized calcium concentration on postoperative days (POD) 1 and 2 after thyroidectomy in the 333 patients studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ionized calcium (mmol/l)</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD 1</td>
<td>1.15</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>POD 2</td>
<td>1.16</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia on POD 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>1.08</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>1.00</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia on POD 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>1.09</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>1.02</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Comparison of mean ionized calcium concentration between the preoperative period and POD 1 and 2 in the 333 patients with or without hypocalcemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Comparison</th>
<th>Difference between means (mmol/l)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without hypocalcemia (n = 197; 59.2%)</td>
<td>Pre × POD 1</td>
<td>0.036</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Pre × POD 2</td>
<td>0.034</td>
<td>0.000</td>
</tr>
<tr>
<td>With hypocalcemia (n = 136; 40.8%)</td>
<td>Pre × POD 1</td>
<td>0.178</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Pre × POD 2</td>
<td>0.170</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypocalcemia (without × with avras03 symptoms)</td>
<td>POD 1 without × POD 1 with</td>
<td>0.080</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>POD 2 without × POD 2 with</td>
<td>0.070</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Student’s t-test

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*Pre* preoperative ionized calcium concentration
Postoperative hypocalcemia has been a subject of investigation since the last century and continues to be controversial until today [1–5]. The lack of consensus regarding the definition of transient hypocalcemia impairs the comparison of the incidence of this condition between studies. Some authors distinguish asymptomatic hypocalcemia from hypoparathyroidism, whereas others define only symptomatic cases as hypocalcemia [6, 7]. There are surgeons who routinely administer calcium to patients after total thyroidec- tomy, and this masks the results and alters the incidence of asymptomatic and symptomatic hypocalcemia [6, 7]. Furthermore, reference values vary according to the measurement technique used, which differs among studies [8].

Hemodilution is known to play an important role in the alteration of plasma electrolyte concentrations, leading to a transient postoperative decrease of calcium, phosphorus, and magnesium, as well as albumin levels and pH [9, 10]. The release of antidiuretic hormone in response to surgical stress and the consequent retention of water are some of the factors responsible for hemodilution [11]. At the end of surgery, PTH levels increase to compensate for the loss of calcium [12].

As a result of hemodilution, the use of either total calcium or ionized calcium for the evaluation of hypocalcemia is another confounding factor. Approximately 99% of total skeletal calcium is found in the form of hydroxyapatite crystals \([\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\). Only 1% of bone calcium is freely exchanged with the extracellular fluid under the stimulus of PTH, and serves as a rapid buffering mechanism, preventing an excessive increase or decrease of calcium concentration in extracellular fluids [10, 13]. Because ionized calcium is almost exclusively influenced by PTH, its measurement is of greater relevance for the evaluation of hypocalcemia [10, 13, 14].

In the present study, we evaluated the presence or absence of hypocalcemia classified into transient hypocalcemia (presence or absence of symptoms) and definitive hypoparathyroidism. For this reason, one of the exclusion criteria was preoperative ionized calcium levels below normal, which, despite being physiological, may alter or confound the postoperative results. Patients with ionized calcium above normal levels were therefore excluded from the study after the measurement of PTH to confirm the presence of hyperparathyroidism.

During the postoperative period laboratory tests were performed at 6:00 a.m. to maintain a pattern in the blood-collection schedule for all patients. The dates for outpatient return were those previously defined in the management protocol of the Service; thus, new ionized calcium measurements were carried out on POD 30. The maximum period for the definition of definitive hypoparathyroidism considered by our Service and in the protocol of this study was 180 days after surgery. Thus, the patients were scheduled to return within this period for the measurement of ionized calcium and PTH. The intermediate date of 90 days was defined in order to identify among patients with hypocalcemia those whose calcium levels would return to baseline values within a period of less than 6 months.

In the present study, we observed a decrease in mean ionized calcium concentration in all patients submitted to thyroidectomy, irrespective of the extent of surgery or histological type. The extent of the surgical procedure was directly related to the incidence of hypocalcemia, although minor surgeries may result in a decline of serum calcium. We observed a direct relationship between diseases that require more aggressive treatment and a significantly higher incidence of hypocalcemia. This finding agrees with data obtained by other investigators who reported the influence of hemodilution on perioperative and postoperative ion concentration. The decline in ionized calcium was

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**Table 3** Estimate of mean ionized calcium concentration for the 136 hypocalcemic patients with and without symptoms by means of the 95% confidence interval

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mean ionized calcium (mmol/l)</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower (mmol/l)</td>
<td>Upper (mmol/l)</td>
</tr>
<tr>
<td>POD 1 Without symptoms</td>
<td>1.08</td>
<td>1.07</td>
</tr>
<tr>
<td>With symptoms</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>POD 2 Without symptoms</td>
<td>1.09</td>
<td>1.07</td>
</tr>
<tr>
<td>With symptoms</td>
<td>1.02</td>
<td>0.99</td>
</tr>
</tbody>
</table>
significantly higher in patients who required calcium replacement therapy than in asymptomatic patients. This finding suggests that other factors might be involved in the development of hypocalcemia after thyroideectomy, including a lack or reduction of PTH resulting from parathyroid gland dysfunction.

In thyroideectomy, the endocrine-metabolic response is usually discrete and short lasting. Consequently, both volume status and ion concentrations rapidly return to the preoperative basal state [10, 13, 14]. Measurement of ionized calcium on the first two days after operation allows observation, to some degree, of the reestablishment of volume status and calcium concentration. The amount of calcium that can be exchanged between bone and extracellular fluid also prevents a greater loss of ionized calcium as long as the PTH stimulus is maintained.

One aspect specific to thyroideectomy is the involvement of the parathyroid glands during operation. When all glands are affected as a result of damage to their vascular pedicle, inadvertent resection, or manipulation, an important decline in PTH levels occurs, leading to earlier and more intense hypocalcemia and consequent symptoms. The partial maintenance of parathyroid function results in a less expressive decrease in PTH, which persists until the recovery of adequate production of this hormone after operation, either from hyperplasia of remnant glands when only one gland is resected or from cell repair in multiple glands that became ischemic as a result of surgical trauma. The less expressive decline in PTH contributes to postoperative hypocalcemia. However, because the reduction is lower, the decline in calcium concentration is slower and less intense, and therefore it does not cause clinical manifestations. Hemodilution causes a loss of calcium, especially total calcium, and the reduced or absent PTH stimulus contributes to the fact that ionized calcium concentration is corrected more slowly or remains low until PTH levels return to normal or calcium is replaced orally.

Asymptomatic hypocalcemia was not a factor predisposing to definitive hypoparathyroidism, probably because the parathyroid glands “stunned” by surgical trauma recovered their function, or because other parathyroid glands took over the production of PTH necessary for the maintenance of calcium homeostasis. Although the mean ionized calcium concentration at 30 days was within normal limits in patients who developed asymptomatic hypocalcemia, these values were below preoperative levels and this difference was statistically significant. The return of basal parathyroid function, with the production of PTH necessary for calcium homeostasis, was found to be slower, with ionized calcium levels returning to normal only 30 days after surgery. Only patients with symptomatic hypocalcemia progressed to definitive hypoparathyroidism, a finding that supports the hypothesis that the loss of postoperative calcium is associated with parathyroid gland dysfunction.

Many surgeons prolong the time of hospitalization in order to monitor postoperative calcium levels and to prevent patient readmissions for symptomatic hypocalcemia [15]. According to Roh and Park [16], post-thyroideectomy monitoring of calcium to predict hypocalcemia is not an effective method to ensure short hospital stays because the onset of clinical manifestations is often delayed. Lo [17] suggested that postoperative monitoring of serum calcium should be reserved for patients undergoing bilateral procedures or reoperation, because there is an increased risk of postoperative hypocalcemia in these cases. Some investigators have proposed monitoring of patients after thyroideectomy by serial measurement of calcium at 6, 12, and 20 h or 8, 14, and 20 h after operation [18, 19]. In view of the difficulties in identifying true predictive factors, other authors have suggested sending the patient home with a prescription for continuous routine use of oral calcium, with or without oral vitamin D [7].

Recent studies have validated the role of postoperative PTH measurement alone or in combination with calcium in an attempt to prevent symptoms of hypocalcemia [3, 5, 15, 19, 20]. This approach is adopted because it is frequently not possible to predict which patients will develop hypocalcemia based only on their preoperative characteristics or intraoperative findings. Lombardi et al. [4], studying 523 patients by serial measurement of PTH and calcium, concluded that, due to the lack of other safe and more sensitive and accurate tests, monitoring serum calcium remains the gold standard for the identification of cases of post-thyroidectomy hypocalcemia. In the same study, PTH levels (measured 4 h after surgery) ranged from 28.8 ± 15.3 pg/ml in normocalcemic patients to 11.2 ± 11.6 pg/ml in hypocalcemic patients (P < 0.001), but the intersection of values between the two groups impaired the calculation of a cut-off value.

In an Australian study, normal intact PTH measured 4 h after the end of surgery presented 92.6% sensitivity and 70.7% specificity in predicting normocalcemia, whereas the sensitivity of low PTH in predicting hypocalcemia was 70.7% and specificity was 92.6% [21]. The study suggested discharge from the hospital on the first day after surgery for patients submitted to total thyroideectomy when PTH was normal.

Few services in Brazil use immunochemiluminescence for the rapid assessment of intact PTH. The technique currently used by laboratories in Belo Horizonte and by the University Hospital of UFMG is sequential chemoluminescence, which yields results within 2 h after sample preparation. The main problem is that this test has to be performed at least every 2 days, depending on the number of samples to be analyzed. Probably, ultra-rapid PTH
determination combined with ionized calcium measurement will become the gold standard for the early diagnosis of post-thyroidectomy hypocalcemia and hypoparathyroidism. Meanwhile, well-designed assays are necessary to define the best time to perform these two tests, obviously assuming that they are available for clinical routine. According to Higgins et al. [22], although postoperative PTH determination might be indicated for patients who are at risk of developing hypocalcemia, the test alone, without the measurement of calcium, is insufficient.

The present study was conducted according to the routine of our Service, which has included for some years the preoperative and postoperative determination of ionized calcium to allow diagnosis of postoperative hypocalcemia and to institute treatment when indicated. Taking into account mainly economic factors, PTH measurement is not routinely employed and is reserved only for the diagnosis of hyperparathyroidism or late confirmation (after 6 months) of definitive hypoparathyroidism. We therefore tried to determine an ionized calcium cut-off that could predict which patients would develop symptoms after thyroidectomy. We observed that 95% of the patients with postoperative ionized calcium levels below 1.03 mmol/l on POD 1 and below 1.05 mmol/l on POD 2 may develop symptoms of hypocalcemia. Patients presenting higher levels would rarely develop symptoms and could be discharged more safely. Although rare, patients with ionized calcium level above the lower normal limit on POD 1 may progress to hypocalcemia on the second day, but only 1% of these patients would present symptoms.

We conclude that ionized calcium concentrations of less than 1.03 mmol/l on POD 1 and less than 1.05 mmol/l on POD 2 are indicative of symptomatic hypocalcemia and the need for calcium administration. Patients with a calcium concentration higher than 1.07 mmol/l are asymptomatic. Progression to definitive hypoparathyroidism is only observed in patients with clinical manifestations of hypocalcemia. Measurement of ionized calcium on POD 1 and POD 2 is sufficient to evaluate hypocalcemia after thyroidectomy.

References