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Total Thyroidectomy: Is there a Link between Thyroid Pathology and Secondary Hypocalcemia?

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Abstract

Introduction: Early and persistent hypocalcemia is a complication of total thyroidectomy. Our study aims to investigate the variations of this biological marker according to the nature of the operative indication.

Materials and Methods: A single-center, retrospective study was carried out over a 4-year period. A total of 282 patients undergoing total thyroidectomy were included in the study. The operative indications were: Malignant tumor (45 patients), thyrotoxicosis (105 patients) or compressive goiter (132 patients).

Objectives: The primary objective of the study was to determine whether patients with toxic goiter had a significantly higher risk of developing hypocalcemia at different postoperative time points (at 2 days then 1 and 6 months). The secondary objectives were to investigate the association between the discovery of incidental parathyroid on histological examination of the specimen and secondary hypocalcemia, to assess the risk of secondary hypocalcemia according to the ligation technique used, and to determine the risk factors for hypocalcemia at different postoperative times.

Results: Early hypocalcemia was observed in 83 patients (30.15%). It persisted at 1 month in 22 patients (8%) and at 6 months in 8 patients (2.8%). Patients operated on for toxic goiter showed a significant decrease in early Calcemia (p=0.015), but no significant decrease at 1 month (p=0.14) or 6 months (p=0.09) compared to patients operated on for compressive goiter. There were no more incidental parathyroid removals in the group of patients operated on for toxic goiter than in those operated on for compressive goiter (p=0.96). The number of incidental parathyroidectomies was higher in the malignant group than in the toxic goiter group (p=0.04). There was significantly more early hypocalcemia at D2 when using LigaSure compared to wire or clip ligation (p=0.020). Factors significantly associated with an increased risk of permanent hypocalcemia at 6 months were lower mean age (41.4 ± 16.2 years vs. 53.1 ± 15.6 years; p=0.037), the presence of one or more parathyroids on pathology (p=0.017), the existence of symptomatic hypocalcemia (p<0.001), or rehospitalization for hypocalcemia (p=0.001).

Conclusion: Our study shows an increased risk of early hypocalcemia in patients undergoing total thyroidectomy for thyrotoxicosis and when using the LigaSure. The risk of parathyroid devascularization in patients with toxic goiter warrants careful dissection and coagulation during surgery.

Keywords: Total thyroidectomy; Secondary hypocalcemia; Thyrotoxicosis; Ligation technique; Permanent hypocalcemia

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Introduction

Total thyroidectomy is a widely practiced surgical procedure for different operative indications. In France 48,000 total thyroidectomies were performed in 2012. The trend has been towards a decrease in the number of procedures, with 42,000 performed in 2016, according to Figure 1 provided by the French Academy of Medicine [1]. The indication for surgery may correspond to the radical control of a hyperthyroidism that has become toxic, in spite of a well-managed medical treatment, as in the case of Graves' disease. Two other classic indications are multi-nodular and compressive non-toxic goiter and thyroid cancer.

The early and distant complications of this surgery are essentially constituted by a risk of laryngeal paralysis evaluated between 0% and 5%, the occurrence of permanent hypocalcemia in less than 3% of cases and the appearance of a hematoma (0-6.5%) according to the data in the literature [2-5].

Our work focused on the hypocalcemia resulting from hypoprothrombinemia and on the variation of this biological marker according to the surgical indication.

We studied the risks of developing early hypocalcemia at D2, persistent at 1 month but also permanent at more than 6 months depending on the operative indication.

The primary objective of the study was to determine whether patients with toxic goiter had a significantly higher risk of developing hypocalcemia at the different postoperative times (at D2, 1 and 6 months).

Secondary objectives were to investigate the association between the discovery of incidental parathyroid on histological examination of the specimen and secondary hypocalcemia, to assess the risk of secondary hypocalcemia according to the ligation technique used, and to determine the risk factors for hypocalcemia at the different postoperative times.

We also assessed the length of hospital stay, the occurrence of secondary hospitalization, the duration of the procedure, the occurrence of clinical signs of hypocalcemia, the occurrence of hematoma or infection.

Finally, the last point was to characterize the patients most likely to develop permanent hypocalcemia, i.e., persistent for more than 6 months after the operation.

Materials and Methods

Study population and objectives

This was a retrospective, single-center study conducted at a university hospital.

The main objective was to determine whether patients with toxic goiter had a significantly higher risk of developing hypocalcemia at different post-operative times (early, 1 and 6 months). For this purpose, we compared successively patients operated for toxic goiter and those operated for either of the following indications: Multi-hetero-nodular goiter or cancerous nodule.

The secondary objectives were:

- To search for an association between the discovery of incidental parathyroid on histological examination of the specimen and secondary hypocalcemia,
- To show that the ligation technique used does not alter the risk of developing persistent or permanent postoperative hypocalcemia,
- To determine the risk factors for hypocalcemia at the various postoperative stages.
- The list of patients was established on the reference software between January 01st, 2015 and December 31st, 2018, based on the following quotation procedures: KCFA005 (total thyroidectomy by Cervicotomy), KCFA007 (total thyroidectomy by Cervicothoracotomy) or KCMA001 (secondary totalization of thyroidectomy by Cervicotomy).

The procedure was performed by either ENT or digestive surgeons, all of whom were familiar with this type of surgery. The distribution of procedures was as follows, after application of the exclusion criteria: 248 patients operated on by ENT surgeons and 34 patients by digestive surgeons.

The exclusion criteria were as follows:

- Patients operated on by simple thyroid lobo-isthmectomy with one lobe remaining,
- Patients undergoing parathyroidectomy associated with total thyroidectomy,
- Patients operated on for total laryngectomy associated with total thyroidectomy,
- Coding errors,
- Patients lost to follow-up before 6 months post-operatively
- The patients' files had to include the following information
- Corrected serum calcium at D2 (failing that, at D1), at 1 and 6 months following the initial corrected serum calcium,
- An operative report including the ultra-ligation technique used, whether or not a mediastino-recurrent courage was performed, the parathyroid seen intraoperatively,
- The report of the anatomopathological analysis including the final histology of the excision specimen with the confirmation of the thyroid pathology as well as the number of removed parathyroid glands,
- The duration of the operation,
- Duration of hospitalization and occurrence of secondary re-hospitalization
- The occurrence or non-occurrence of clinical signs of hypocalcemia,
- Occurrence of postoperative hematoma or infection and time to onset.

Protocol

The determination of Parathyroid Hormone (PTH) at H6 has become almost systematic in most centers to date [6-8]. However, it was not measured in this series of patients. Vitamin and calcium supplementation was therefore based on the blood calcium level measured at D2.

Corrected serum calcium was calculated from the albumin or blood protein levels according to the following formula:

- Corrected Ca = Measured blood calcium + 0.025 (40-albumin),
- Corrected Ca = Measured Ca/(0.55 + protein/160),

Calcemia was expressed in mmol/L, and albumin and protein were expressed in g/L.

In our study, a blood calcium level below 2 mmol/L was used to define biological hypocalcemia [9-10].

The following definitions were used according to the time at which this biological hypocalcemia was present [11-13]:

- Early if present at D2
- Persistent if present at M1

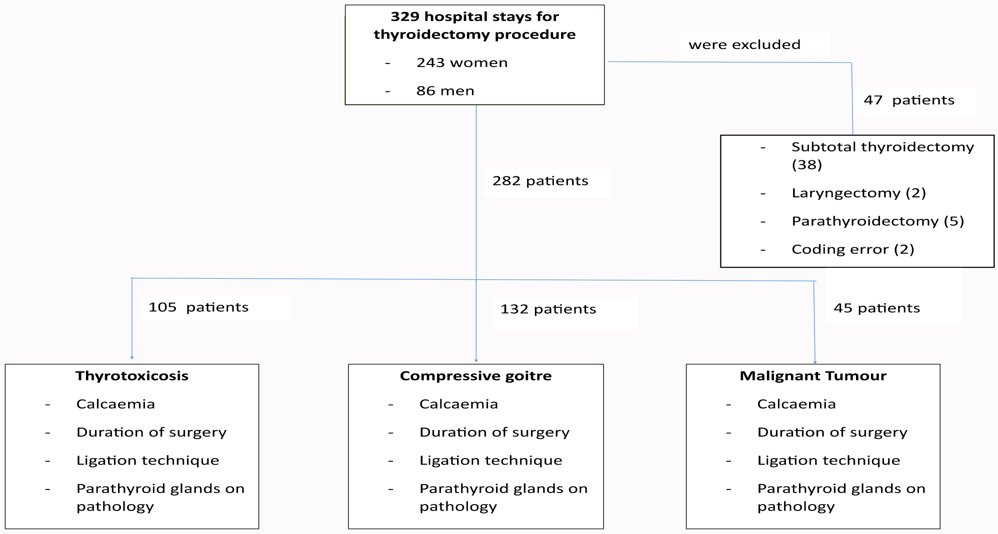

Figure 1: Flow Chart.

- Permanent if present at M6

Vitamin and calcium supplementation concerned patients whose blood calcium level was less than 1.9 mmol/L on D2. It included oral calcium at a dose of 3 g/day and 1alpha-hydroxylated vitamin D (Un-Alfa) at a dose of 3 micrograms/day.

The use of laryngeal neuromonitoring is systematic during all operations and mentioned in the operative report of each operation.

At the end of the operation, unless otherwise stated in the operative report, no Redon drain was placed in the thyroidectomy space.

The immediate postoperative blood glucose levels on Day 2 or Day 1, if applicable, were measured by the automated laboratory of the University Hospital.

The Calcemia at 1-month post-op was measured in different laboratories and the results were brought by the patient to the control consultation with his surgeon. This test was only performed when there was immediate postoperative hypocalcemia.

Calcemia at 6-months was measured when there was persistent hypocalcemia at 1-month and follow-up was then ensured by the endocrinologists.

Statistical analysis

The statistical tests used were the student's t test for quantitative variables to compare two groups together and the Chi^2 test to compare qualitative variables with 2 study factors (for the number of parathyroid found in pathological analysis and for the Calcemia at 1 and 6 months). The Fischer test was used when the expected number of patients was less than 5 instead of the Chi^2 test. A value of $p<0.05$ was conventionally retained as statistically significant.

Results

Characteristics of the population

The initial database consisted of 329 stays for a thyroidectomy procedure.

The following patients were excluded due to concomitant subtotal thyroidectomy (38), associated total laryngectomy (2), associated parathyroidectomy (5), coding error (1) and duplicate (1).

A total of 282 patients undergoing total thyroidectomy (263) or secondary totalization (19) were included in the study. There were 208 women and 74 men, with ages ranging from 12 to 91 years. The indications for surgery were malignancy (45 patients), thyrotoxicosis (105 patients) or compressive goiter (132 patients) Figure 1.

The characteristics of the patients included in the study are summarized in Table 1.

Early hypocalcemia was observed in 85 patients (30.15%). It persisted at 1-month in 23 patients (8%) and at 6-months in 8 patients (2.8%).

Primary endpoint

We successively compared two by two the operative indications "compressive goiter" and "malignant tumor" with the indication "thyrotoxicosis".

First, we compared patients operated for medically resistant thyrotoxicosis with those operated for compressive goiter. The early Calcemia at D2 was significantly lower in the thyrotoxicosis group (p=0.015). On the other hand, we did not find a significant decrease in blood calcium levels at 1-month (p=0.14) or at 6-months (p=0.09) between the two groups (Table 2).

There were no more incidental parathyroid removals in the group of patients operated on for toxic goiter than in those operated on for compressive goiter (p=0.96).

In a second step, we compared patients operated for resistant thyrotoxicosis versus those operated for malignant thyroid nodule. There was no significant difference in the early Calcemia measured at D2 (p=0.231), nor in the number of persistent hypocalcemia at 1-month (p=1.00) or 6-months (p=1.00) between the two groups (Table 3).

There were significantly more incidental parathyroidectomies (p=0.046) in the group of patients operated on for malignancy.

Secondary endpoints

The mean operating time was also recorded. There was no significant difference in operative time for patients operated on

Table 1: Characteristics of the patients.

Characteristics	Population (n=282)	Thyrotoxicosis (n=105)	Compressive goiter (n=132)	Malignant tumor (n=45)
Sex (n%)	74 (26.2)	23 (21.9)	38 (28.8)	13 (28.9)
Men	208 (73.8)	82 (78.1)	94 (71.2)	32 (71.1)
Women	53.0 ± 15.9	49.5 ± 16.2	55.5 ± 15.2	53.9 ± 15.9
Age (Years) (average ± δ)	75.1 ± 19.3	69.7 ± 21.4	77.1 ± 17.0	79.0 ± 18.6
Weight (Kg) (average ± δ) (n=267)	27.6 ± 10.3	25.5 ± 6.8	28.9 ± 13.1	28.39 ± 6.6
Type (n, %)				
Surgery in one time	262 (92.9)	104 (99.1)	123 (93.2)	35 (77.8)
Totalization of thyroidectomy	20 (7.1)	1 (0.9)	9(6.8)	10 (22.2)

Table 2: Patients operated on resistant thyrotoxicosis.

Comparted Patients operated on medically resistant thyrotoxicosis with those operated on for compressive goiter				
Characteristics	**Population (n=282)**	**Thyrotoxicosis (n=105)**	**Compressive goiter (n=132)**	**Malignant tumor (n=45)**
Hospital length of stay (days) (average ± δ)	3.3 ± 4.0	3.9 ± 5.3	2.8 ± 2.5	0.004
Surgery time (min) (average ± δ) (n=227)	96.5 ± 38.4	96.6 ± 32.6	96.3 ± 42.7	0.947
Parathyroid on pathology (n, %) (n=236)				0.960
0	188 (79.7)	89 (79.8)	105 (79.6)	
1 or more	48 (20.3)	21 (20.2)	27 (20.5)	
Ligation technique (n, %) (n=180)				0.743
LigaSure	157 (87.2)	74 (88.1)	83 (86.5)	
Vascular clips	23 (12.8)	10 (11.9)	13 (13.5)	
Hematoma (n, %)	8 (3.4)	2 (1.9)	6 (4.6)	0.307
Surgery site infection (n, %)	5 (2.1)	3 (2.91)	2 (1.5)	0.658
Calcemia at D2(mmol/L) (average ± δ) (n=223)	20.3 ± 0.20	19.9 ± 0.22	20.6 ± 0.18	0.011
Corrected Calcemia at D2(mmol/L) (average ± δ)	21.0 ± 0.22	20.6 ± 0.24	21.3 ± 0.18	0.015
Hypocalcemia M1 (n, %)	18 (7.6)	11 (10.5)	7 (5.3)	0.140
Hypocalcemia M6 (n, %)	6 (2.5)	5 (4.8)	1 (0.8)	0.091
Symptomatic hypocalcemia (n, %)	27 (11.4)	19 (18.1)	8 (6.1)	0.004
Rehospitalization for hypocalcemia (n, %)	8(3.4)	6(5.7)	2(1.5)	0.143
Calcium supplementation at D2 (mmol/L) (n, %)	73(30.8)	38(36.3)	35(26.5)	0.109
Comparted Patients operated on resistant thyrotoxicosis versus those operated on for malignant thyroid nodules				
Characteristics	**Population (n=282)**	**Thyrotoxicosis (n=105)**	**Malignant tumor (n=45)**	**p-value**
Hospital length of stay (days) (average ± δ)	3.5 ± 4.5	3.9 ± 5.3	2.6 ± 1.4	0.017
Surgery time (min) (average ± δ) (n=142)	100.5 ± 41.5	96.6 ± 32.6	110.5 ± 57.7	0.160
Parathyroid on pathology (n, %) (n=149)				0.046
0	112 (75.2)	89 (79.8)	29 (64.4)	
1 or more	37 (24.38)	21 (20.2)	16 (35.6)	
Ligation technique (n, %) (n=117)				0.505
LigaSure	105 (89.7)	74 (88.1)	31 (93.9)	
Vascular clips	12 (10.3)	10 (11.9)	2 (6.1)	
Hematoma (n, %)	2 (1.3)	2 (1.9)	0 (0.0)	1.000
Surgery site infection (n, %)	6 (4.0)	3 (2.91)	3 (6.7)	0.365
Calcemia at D2 (mmol/L) (average ± δ) (n=140)	19.8 ± 0.20	19.9 ± 0.22	19.6 ± 0.16	0.292
Corrected Calcemia at D2 (mmol/L) (average ± δ)	20.5 ± 0.22	20.6 ± 0.24	20.2 ± 0.17	0.231
Hypocalcemia M1 (n, %)	16 (10.7)	11 (10.5)	5 (11.4)	1.000
Hypocalcemia M6 (n, %)	7 (4.7)	5 (4.8)	2 (4.6)	1.000
Symptomatic hypocalcemia (n, %)	23 (15.3)	19 (18.1)	4 (8.9)	0.152
Rehospitalization for hypocalcemia (n, %)	7 (4.7)	6 (5.7)	1 (2.2)	0.675
Calcium supplementation at D2 (mmol/L) (n, %)	53 (36.7)	38 (36.3)	17 (37.8)	0.853

Table 3: Influence of the ligation technique.

Characteristics	Population(n=213)	LigaSure (n=188)	Vascular clips (n=25)	P-Value
Calcemia at D2 (mmol/L) (average ± δ) (n=223)	20.2 ± 0.20	20.2 ± 0.20	20.6 ± 0.20	0.418
Corrected Calcemia at D2 (mmol/L) (average ± δ)	2.09 ± 0.21	2.08 ± 0.21	2.18 ± 0.17	0.020
Hypocalcemia M1 (n, %)	18 (8.5)	14 (7.5)	4 (16.0)	0.240
Hypocalcemia M6 (n, %)	8 (3.8)	6 (3.2)	2 (8.0)	0.240

Table 4: Risk factors for developing Hypocalcemia.

Risk factors for developing persistent hypocalcemia (M1)				
Characteristics	**Population (n=280)**	**No hypoM1 (n=257)**	**HypoM1 (n=23)**	**P-Value**
Age (Years) (average ± δ)	52.8 ± 1.57	53.3 ± 15.7	47.8 ± 15.0	0.110
Weight (Kg) (average ± δ) (n=267)	75.0 ± 19.4	74.2 ± 19.4	84.2 ± 17.6	0.024
BMI (average ± δ) (n=265)	27.6 ± 10.3	27.4 ± 10.6	29.4 ± 6.1	0.191
Surgery time (min) (average ± δ) (n=265)	97.6 ± 3.92	95.8 ± 38.3	116.4 ± 44.4	0.016
Parathyroid on pathology (n, %)				0.015
0	215 (77.1)	202 (78.9)	13 (56.5)	
1 or more	64 (22.9)	54 (21.1)	10 (43.5)	
Symptomatic hypocalcemia (n, %)	30 (10.7)	19 (7.4)	11 (47.8)	<0.001
Rehospitalization for hypocalcemia (n, %)	9(3,2)	5(2,0)	4(17,4)	0,003
Calcium supplementation at D2 (mmol/L) (n, %)	89(31,8)	69(26,9)	20(87,0)	<0,001
Risk factors for developing permanent hypocalcemia (M6)				
Characteristics	**Population(n=280)**	**No HYpoM6(n=272)**	**HypoM6(n=8)**	**P-Value**
Age (Years) (average ± δ)	52.8 ± 1.57	53.1 ± 15.6	41.4 ± 16.2	0.037
Weight (Kg) (average ± δ) (n=267)	75.0 ± 19.4	74.8 ± 19.3	85.0 ± 24.0	0.168
BMI (average ± δ) (n=265)	27.6 ± 10.3	27.5 ± 10.4	29.2 ± 7.3	0.662
Surgery time (min) (average ± δ) (n=265)	97.6 ± 3.92	96.9 ± 39.1	117.5 ± 39.9	0.144
Parathyroid on pathology (n, %)				0.017
0	215 (77.1)	212 (78.2)	3 (37.5)	
1 or more	64 (22.9)	59 (21.8)	5 (62.5)	
Symptomatic hypocalcemia (n, %)	30 (10.7)	25 (9.2)	5 (62.5)	<0.001
Rehospitalization for hypocalcemia (n, %)	9 (3.2)	6 (2.2)	3 (37.5)	0.001
Calcium supplementation at D2 (mmol/L) (n, %)	89 (31.8)	81 (29.8)	8 (100.0)	<0.001

for toxic goiter compared to those operated on for compressive goiter (p=0.947) or compared to those operated on for removal of a malignant nodule (p=0.160).

On the other hand, patients managed for a toxic goiter had a significant increase in their length of stay after surgery (p=0.044; *vs.* compressive goiter and p=0.017 *vs.* malignant nodule).

The occurrence of a hematoma, for all indications combined, was 8 per 282, i.e., a rate of 2.8% in our series. The occurrence of a surgical site infection was also 8 per 282 patients, i.e., 2.8% (Table 2, 3).

The incidence of hematoma or infection was not greater in the toxic goiter group than in the compressive goiter or malignant thyroid nodule group.

Regarding the ligation technique used, we compared the use of LigaSure (n=188 patients) and the use of traditional ligation either with absorbable sutures or vascular clips (n=25). Patients whose operative report did not specifically mention the vascular ligation technique used was excluded.

There was significantly more early hypocalcemia on Day 2 when using LigaSure compared to wire or clip ligation (p=0.020). This difference was no longer observed at 1 month (p=0.240) or 6-months postoperatively (p=0.240) (Table 4).

The management of secondary hypocalcemia was observed using the following 3 data: Initiation of calcium supplementation, existence of symptomatic hypocalcemia or secondary rehospitalization for hypocalcemia (Table 2, 3).

There was no difference in these three parameters between patients with thyrotoxicosis and patients operated on for a malignant nodule.

On the other hand, we found more symptomatic hypocalcemia in patients with toxic goiter than in those operated on for compressive goiter (p=0.004). There was no significant difference between these two groups in terms of eventual rehospitalization or initiation of vitamin and calcium supplementation.

A final objective was to investigate the risk factors for developing persistent or permanent hypocalcemia.

The following factors were significantly associated with an increased risk of persistent hypocalcemia at 1-month male gender (p=0.047), greater mean weight (84.2 ± 17.6 kg *vs.* 74.2 ± 19.4 kg; p=0.024), longer operative time (116.4 ± 44.4 min *vs.* 95.8 ± 38.3 min; p=0.016), the presence of one or more parathyroids on pathology (p=0.015), the presence of symptomatic hypocalcemia (p<0.001) or re-hospitalization for hypocalcemia (p=0.003) (Table 5).

The following factors were significantly associated with an increased risk of permanent hypocalcemia at 6-months: Lower mean age (41.4 ± 16.2 years *vs.* 53.1 ± 15.6 years; p=0.037), the presence of one or more parathyroids on pathology (p=0.017), the presence of symptomatic hypocalcemia (p<0.001) or rehospitalization for hypocalcemia (p=0.001) (Table 6).

Discussion

Thyrotoxicosis and early hypocalcemia

In our retrospective study, we found rates of early hypocalcemia (30.15%), persistent hypocalcemia at 1-month (8%) and permanent hypocalcemia at 6-months (2.8%).

These figures are similar to those found in the literature with a rate of transient hypocalcemia between 0.3 and 65% of cases and permanent hypocalcemia at 6-months in about 3% of cases [3,4,9,14,15].

Based on this initial observation, we were able to look more specifically at the link between thyroid pathology and the development of hypocalcemia secondary to the surgical procedure.

Some recent studies have already considered the risk of developing a postoperative complication, including hypocalcemia, in patients with Graves' disease [4,16-19].

We found that early hypocalcemia was significantly more frequent at D2 in the toxic goiter group than in the compressive goiter group. These results are in agreement with an older retrospective study by Biet et al. [16], whose cohort is of similar size to ours. Similarly, the more recent North American study corroborates this data with a much larger cohort of patients, with 17,906 patients included [4]. In contrast, the study by Hallgrimsson et al. and Chiang et al. found no difference in the occurrence of early hypocalcemia between these two groups [19,20].

These differences could be explained in part by the variation in preoperative premedication protocols in patients with Graves' disease. Achieving clinical and biological euthyroidism prior to total thyroidectomy is essential in patients with Graves' disease in order to limit inflammation and hypervascularization of the gland. This is achieved by a well-conducted medical treatment before surgery. The treatment used varies according to the habits of the centers and the urgency of the operation. Most of the treatments used (synthetic antithyroid drugs, Lugol's solution, glucocorticoids, Beta blockers) have a more or less significant preventive action on parathyroid function and therefore a variable impact on early postoperative Calcemia [19,21-23]. Despite this impact on blood calcium levels, the perioperative management of patients with Graves' disease using these treatments is now indisputable. The aim is to avoid the metabolic cataclysm of uncontrolled hyperthyroidism, which can lead to multi-visceral failure and thus increased mortality and morbidity ("thyroid storm") [20].

In patients who have not been able to receive this pre-operative preparation properly or in those who have difficulty achieving euthyroidism, the early hypocalcemia observed may be explained by another phenomenon. Indeed, a high concentration of thyroid hormone in the blood leads to hypermetabolism of bone ("hungry bone"), which is responsible for an increase in calcium uptake in the bone and therefore hypocalcemia [21].

Incidental parathyroidectomy and early hypocalcemia

In contrast, there was no difference in the occurrence of early hypocalcemia at D2 between the thyrotoxicosis and malignant nodule groups. This lack of difference could be explained by the fact that there is a higher proportion of incidental parathyroidectomy in the malignant nodule group (p=0.046). The study by André et al. is in contrast to this proposal and shows that there is no more early hypocalcemia at Day 1 in patients who have had an incidental parathyroidectomy on pathological examination, all surgical indications taken together [24]. All authors agree that these unintentional parathyroidectomies have no impact on early postoperative calcium levels [25-30]. However, André et al. show that early blood calcium levels at day 1 are significantly lower in the group that underwent a mediastinal-recurrent lymph nodal procedure [24].

Is there then a link between thyroid disease and secondary hypocalcemia?

Similarly, hypocalcemia was not found to be more frequent in the thyrotoxic group at 1 or 6 months after surgery compared to the other two groups. Our results are in agreement with the study of Pesce et al. [18], who did not find more hypocalcemia in patients with Graves' disease at 1-month after surgery. In the literature, studies concerning the persistence of hypocalcemia at 6-months following total thyroidectomy for Graves' disease are relatively rare [16]. For example, Biet et al. [16], did not find significantly more permanent hypocalcemia in the Graves' disease group. But the cohort in this study, like ours, is small and it is therefore difficult to show any difference in this criterion given the rarity of permanent hypocalcemia.

Another of our interpretations is that the more frequent occurrence of early hypocalcemia in the Graves' disease group may be due to parathyroid gland sideration during surgery. This may be due to transient ischemia associated with the difficulty of dissecting the thyroid tissue and capsule, which are inflammatory and thickened in this condition [16]. The difficulties of coagulation and hemostasis are then more important in these patients, the thyroid gland and surrounding tissues being much more fragile, friable and hypervascularized. Adhesion between the thyroid capsule and the parathyroid glands is also more pronounced leading to prolonged manipulation of the parathyroid glands [16,21,31,32]. Based on these findings, we were interested in the occurrence of secondary hypocalcemia depending on the vascular ligation technique used during the procedure.

Influence of the ligation technique used

We found that early hypocalcemia occurred more frequently with the use of LigaSure than with the more traditional use of wire or vascular clips. In contrast to our results, the study by Youssef et al., did not find more transient hypocalcemia when using LigaSure compared to wire ligation [33]. Another prospective, randomized study by Pons et al, confirmed the latter results: There was no more transient hypocalcemia regardless of the ligation technique used (LigaSure *vs.* Harmonic clamp *vs.* vascular clips) [34]. The use of the LigaSure remains a safe and effective means of achieving hemostasis during total thyroidectomy with a reduction in operative time and blood loss during the procedure compared to wire ligation. In addition, the usual postoperative complications of this surgery are not more frequent when using the LigaSure [33,35,36].

Length of stay in hospital

The length of hospital stay was also an interesting parameter to take into account. In our study we found that the length of stay was significantly longer in patients with toxic hyperthyroidism.

This is mainly due to the fact that symptomatic hypocalcemia is more frequent in this group than in patients operated on for compressive goiter. But this does not explain the difference observed for patients operated on for a malignant nodule, as there is no more symptomatic hypocalcemia in these patients compared to patients with Graves' disease.

The length of hospital stay is slightly over estimated as 4 patients developed cardio-thyrosis and was admitted to the ICU following surgery. This may constitute a bias; especially as other studies have not found a significant increase in length of stay in Graves' disease [16].

In any case, the length of hospital stays, whatever the indication for surgery, was relatively short in our study, averaging 3.1 days (Table 1). In fact, this duration is evaluated at almost 5 days for all indications combined in the study by Biet et al. [16].

The low rates of surgical complications such as hematoma or surgical site infection lead us to believe that only the problem of secondary hypo parathyroidism is the main reason for the variation in the length of hospital stay. There was no significant difference in the occurrence of postoperative hematoma or infection between the groups (Table 2, 3).

Interest of the study

It is therefore interesting to be able to characterize which patients have a short length of stay and to consider those who could benefit from possible outpatient management.

PTH measurement, which is measured early, usually between H4 and H6 after surgery, is a very interesting parameter to determine patients at risk of developing early hypocalcemia and therefore to supplement them as soon as possible. The protocol currently used in our department is as follows: A PTH of more than 20 pg/mL does not require blood calcium levels to be measured or supplemented, a PTH of less than 10 pg/mL requires immediate supplementation, and a threshold of between 10 and 20 pg/mL requires blood calcium levels to be measured on days 1 and 2 and vitamin and calcium supplementation to be carried out according to the kinetics. In the literature, the threshold of PTH >15 pg/mL is usually retained as the value above which postoperative calcium measurement is not necessary [37].

In our study, this protocol was not yet in place at the time of patient inclusion. PTH measurement is of interest to supplement early hypo-parathyroid patients as early as possible and also to allow discharge on day 1 when parathyroid function is preserved.

In order to further reduce the length of hospitalization, it would be necessary to be able to select a population of patients likely not to present early hypocalcemia in parallel of course with the PTH assay. This assay would then only make it possible to validate the same-day discharge of these patients. Hence the interest in having a target population to be managed on an outpatient basis, otherwise we will have to convert outpatient hospitalization into traditional hospitalization for patients with low PTH. Of course, other data must be taken into account in this management decision, notably the experience of the operator.

We have seen that patient with Graves' disease or at least thyrotoxicosis has a longer hospital stay, partly due to more frequent and symptomatic early hypocalcemia. These patients would therefore not be the most eligible for outpatient surgery.

Outpatient surgery could therefore be considered for patients with benign multi-hetero-nodular goiter or those operated on for the removal of a malignant nodule not benefiting from a mediastino-recurrent courage.

Another point concerns the outcome of patients with hypocalcemia secondary to surgery. We have seen that patients with thyrotoxicosis have a significant increased risk of developing symptomatic hypocalcemia compared to the compressive goiter group [19,38].

This further reinforces the fact that the biological and clinical calcium monitoring of these patients must be careful.

What factors predict secondary hypocalcemia?

The analysis of the predictive factors of hypocalcemia at M1 or M6 was relevant insofar as it allowed us to characterize which patients should benefit from a strict follow-up in the postoperative period. However, here this analysis could lack power due to the lack of numbers in the hypocalcemia group at M1 (23 patients) and at M6 (8 patients).

In our study we found that male gender was a risk factor for hypocalcemia at M1. A study by Del Rio et al. [39], and that of Kazaure et al. [40], affirm that it is the female sex that is predictive of secondary hypocalcemia, but early at D1. Longer operative time and greater weight were associated with a risk of persistent hypocalcemia at M1. In contrast, Body Mass Index (BMI) did not appear to affect the occurrence of persistent hypocalcemia.

The numbers at M6 are logically even smaller than at M1 (8 patients). The analysis of the data nevertheless revealed risk factors for secondary hypocalcemia, which were already present at M1: The presence of one or more parathyroids on pathology ($p=0.017$), the presence of symptomatic hypocalcemia ($p<0.001$) or rehospitalization for hypocalcemia ($p=0.001$). Lower mean age (41.4 ± 16.2 years *vs.* 53.1 ± 15.6 years; $p=0.037$), was significantly associated with a risk of permanent hypocalcemia. This factor was not predictive of hypocalcemia at M1. The incidence of permanent hypocalcemia is not affected by age according to the study by Nair et al. [41]. In the literature, Thomusch et al. [42], analysis of over 5,000 patients identified Graves' disease as an independent risk factor for developing permanent hypocalcemia, which was not found in our study.

Limitations

The biases and limitations of our study lie in the retrospective nature of the analysis. Some data may be missing, such as the accuracy of the type of ligation used. Patients whose operative report did not mention the ligation technique were automatically excluded.

The conditions under which the surgery was performed could differ, particularly in the group of patients operated on for toxic goiter: The procedure could be scheduled cold or performed as an emergency (in cases of cardiothoracic, for example). It is worth adding the difficulty of obtaining clinical and biological euthyroidism pre-operatively in certain patients or the fact of having been "medically prepared" or not before the operation (hyperthyroidism in the context of drug toxicities with unprepared Cordarone, as in the case of Graves' disease). This could be a confounding factor in the interpretation of the data between groups.

Finally, another confounding bias was operator variability even though the dissection techniques used were the same.

Conclusion

In this study we have shown that early hypocalcemia is more frequent in patients whose operative indication is the control of so-called toxic hyperthyroidism compared to patients operated on for benign goiter.

We were able to demonstrate that early hypocalcemia is also more frequent when using LigaSure compared to more traditional ligation techniques such as vascular clips or absorbable wire, regardless of the operative indication.

However, this difference in early hypocalcemia was not significantly different from that observed for Calcemia at 1 and 6 months after surgery.

These results suggest that dissection and coagulation should be performed with caution during total thyroidectomy, particularly in patients with toxic goiter.

Vitamin and calcium supplementation of these patients should be initiated, if necessary, depending on the PTH level, as soon as possible, with the aim of preventing the development of clinical signs of hypocalcemia and reducing the length of hospital stay.

In the future, we may be able to consider outpatient surgery for selected patients who are at lower risk of developing hypocalcemia.

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