

ONCOLOGY

Identification of patients at high risk for hypocalcemia after total thyroidectomy

Identificazione dei pazienti ad alto rischio di ipocalcemia dopo tiroidectomia totale

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SUMMARY

Hypocalcemia is a major post-operative complication of total thyroidectomy, causing severe symptoms and increasing hospitalization time. The primary cause is secondary hypo-parathyroidism following damage to, or devascularisation of, one or more parathyroid glands during surgery. Aim of the study was to develop a simple and reliable method for predicting post-operative hypocalcemia in total thyroidectomy patients. A retrospective analysis was made of immediate pre-operative and early post-operative calcium levels in 100 patients. It was found that a marked decrease in blood calcium, immediately after surgery, was a sensitive predictor of hypocalcemia. In a subsequent prospective series of 67 patients, the efficacy was assessed of early administration of calcium plus Vitamin D in reducing symptomatic hypocalcemia in patients in whom the difference (Δ) between pre- and post-operative blood calcium was ≥ 1.1 mg/dl. This treatment was part of a protocol in which normo-calcemic patients were discharged immediately after drainage removal (third post-operative day).

In the retrospective series, 84% of patients who developed hypocalcemia had $\Delta \geq 1.1$ and 54% of patients who did not develop hypocalcemia had $\Delta < 1.1$ ($p < 0.0001$). Mean duration of hospitalization was 6.2 days. In the prospective series, 76% of patients who developed hypocalcemia had $\Delta \geq 1.1$ mg/dl; of the patients who did not develop hypocalcemia 75% had $\Delta < 1.1$ mg/dl ($p = 0.0013$); mean hospitalization was 4.7 days ($p < 0.0001$). Use of the 1.1 mg/dl cut-off for deciding whether to start early prophylaxis allowed most patients to avoid symptomatic hypocalcemia (and the associated anxiety), while permitting a significantly reduced hospital stay, resulting in lower hospitalization costs.

KEY WORDS: Thyroidectomy • Hypocalcemia • Calcium therapy

RIASSUNTO

L'ipocalcemia è la complicanza post-operatoria più frequente negli interventi di tiroidectomia totale, causando gravi sintomi e aumentando il tempo di ospedalizzazione. La causa principale è l'ipoparatiroidismo secondario dovuto al danneggiamento o alla devascularizzazione di una o più ghiandole paratiroidi durante l'intervento chirurgico. Abbiamo cercato di sviluppare un metodo semplice e affidabile per predire l'ipocalcemia post-operatoria in pazienti sottoposti a tiroidectomia totale. Sono stati analizzati retrospettivamente i livelli di calcemia nell'immediato pre-operatorio e precocemente nel post-operatorio in 100 pazienti. Abbiamo notato che una significativa diminuzione della calcemia subito dopo l'intervento chirurgico era un fattore predittivo di ipocalcemia. In una successiva serie prospettica di 67 pazienti, è stata valutata l'efficacia della somministrazione precoce di calcio più vitamina D per ridurre l'ipocalcemia sintomatica nei pazienti in cui la differenza (Δ) tra il calcio nel sangue pre- e post-operatorio era $\geq 1,1$ mg/dl. Questa terapia faceva parte di un protocollo nel quale i pazienti normocalcemic venivano dimessi immediatamente dopo la rimozione del drenaggio (terza giornata post-operatoria). Nella serie retrospettiva, l'84% dei pazienti che avevano sviluppato l'ipocalcemia aveva $\Delta \geq 1,1$ e il 54% dei pazienti che non mostrava l'ipocalcemia aveva $\Delta < 1,1$ ($p < 0,0001$). La degenza media è stata di 6,2 giorni. Nella serie prospettica, il 76% dei pazienti che aveva sviluppato l'ipocalcemia mostrava un $\Delta \geq 1,1$ mg/dl; dei pazienti che non avevano sviluppato l'ipocalcemia, il 75% aveva un $\Delta < 1,1$ mg/dl ($p = 0,0013$); la degenza media è stata di 4,7 giorni ($p < 0,0001$). L'utilizzo del valore 1,1 mg/dl come cut-off per decidere se avviare precocemente la terapia calcica ha permesso alla maggior parte dei pazienti di evitare l'ipocalcemia sintomatica (e l'ansia ad essa associata), riducendo anche in modo significativo la degenza post-operatoria con conseguente riduzione dei costi di ospedalizzazione.

PAROLE CHIAVE: Tiroidectomia • Ipocalcemia • Terapia calcica

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Introduction

Hypocalcemia remains a major post-operative complication of total thyroidectomy causing potentially severe symptoms and anxiety in affected patients and increasing hospitalization time. Transient hypocalcemia, often

observed after the operation, generally responds favourably to replacement therapy within a few days or weeks¹. Hypocalcemia is considered permanent when it does not return to normal within 6 months (1.3-3% of cases)². The primary cause of hypocalcemia is secondary hypo-parathyroidism following damage to, or devascularisation

of, one or more parathyroid glands during surgery. Erroneous parathyroid removal may also be responsible³⁻¹¹. Risk factors for post-operative hypocalcemia following total thyroidectomy include thyroid gland size, substernal extension of the thyroid, type of thyroid disorder, extent of surgery, and whether re-operation is necessary³⁻¹⁰. Hypocalcemia can be asymptomatic, particularly if calcium levels are only mildly reduced, or symptomatic with typical manifestations such as Chvostek's and Trousseau's signs, muscle spasms and paresthesia. Severe neurological manifestations may occur if the condition is not adequately treated. Post-operative hypocalcemia requires calcium and Vitamin D supplementation, with monitoring until blood calcium returns to normal, thus hospitalisation is typically prolonged. Calcium, with Vitamin D, may be administered for prophylactic purposes but is useless if blood calcium is normal and carries the risk of triggering hypercalcemia.

The aims of the present study were two: a) identify patients at high risk of developing hypocalcemia following total thyroidectomy by means of retrospective analysis of early post-operative calcium levels; b) to assess the efficacy of early prospective administration of calcium and Vitamin D in reducing symptomatic post-operative hypocalcemia and hospitalization time¹⁰ in patients considered at high risk of developing hypocalcemia based on the findings of the retrospective study.

Materials and methods

A retrospective analysis was made of pre- and post-operative calcium levels in 100 consecutive patients who had been submitted to total thyroidectomy at the Thyroid Unit, Division of Head and Neck Surgery, European Institute of Oncology, between 2002 and 2004. From 2006 to 2007, 93 consecutive patients were studied prospectively.

The inclusion criterion for both series was total thyroidectomy with or without neck/level VI dissection. Exclusion criteria were: abnormal serum albumin (above or below the normal range of 3.4-4.8 g/dl), abnormal pre-operative calcium (above or below the normal range of 8.0-10.4 mg/dl (2.00-2.6 mmol/l) in the retrospective series, and 8.8-10.2 mg/dl in the prospective series); abnormal pre-operative parathyroid hormone levels (above or below the normal range of 9.5-75 pg/ml); renal insufficiency and pre-operative calcium replacement.

In all retrospective cases, the following parameters were assessed: pre- and post-operative serum calcium levels (morning and afternoon of all post-operative hospitalization days), presence of one or more parathyroid glands in the surgical specimen, presence of post-operative signs and symptoms of hypocalcemia, post-operative day on which patient became symptomatic (when calcium and Vitamin D supplementation started) and hospitalization time.

Patients operated upon after 2005 were monitored according to a new schedule established following an analysis of outcomes in the retrospective series. Hypocalcemia, number of blood calcium determinations, hospitalization time, and treatment costs were compared in the retrospective and prospective series.

Results

Retrospective series

Mean duration of hospital stay was 6.19 days (standard deviation 0.24), including one day prior to surgery. All patients had normal (9.5-75 pg/ml) pre-operative parathyroid hormone and normal calcium levels (8.0-10.4 mg/dl). A total of 50 (50%) patients developed hypocalcemia (< 8.0 mg/dl) after surgery, of these 24 were symptomatic and 26 asymptomatic (Table I). Of the 24 patients who developed symptomatic hypocalcemia, 3 (12.5%) did so on the first day after surgery. A total of 24 patients developed symptomatic hypocalcemia, 3 (12.5%) on the first day after surgery, 15 (62.5%) on the second day, 4 (17%) on the third day and one (4%) each on the fourth and fifth days (Table II). In all cases, treatment was started on the same day as onset of symptoms and consisted of a single i.v. administration of calcium gluconate (40 mEq in 100 ml physiological solution) with subsequent twice daily oral administration of calcium and Vitamin D. Of the patients who developed asymptomatic hypocalcemia,

Table I. Frequency of hypocalcemia in retrospective and prospective series of patients undergoing total thyroidectomy.

	Retrospective series	Prospective series
Total number of patients (%)	100	67
Number hypocalcemic (%)	50 (50%)	55 (82.1%)
Number symptomatic (%)	24 (24%)	13 (19.4%)
Number asymptomatic (%)	26 (26%)	41 (61.2%)
Not assessed (%)	0 (0%)	1 (1.5%)

Table II. Distribution of appearance of hypocalcemia in the 50 retrospective patients who developed symptomatic or asymptomatic hypocalcemia.

Appearance of hypocalcemia (start of calcium therapy)	Number (%) of patients with symptomatic hypocalcemia	Number (%) of patients with asymptomatic hypocalcemia
First day	3 (12.5%)	1 (4%)
Second day	15 (62.5%)	8 (31%)
Third day	4 (17%)	7 (26%)
Fourth day	1 (4%)	2 (8%)
Fifth day	1 (4%)	0
No post-op. Ca therapy	0	8 (31%)
Total	24	26

one (4%) started treatment on the first, 8 (31%) on the second, 7 (26%) on the third, and 2 (8%) on the fourth post-operative day; in all cases, on account of abnormally low calcium levels. Eight of the 26 (31%) asymptomatic hypocalcemic patients were not treated.

A total of 26 (26%) patients had parathyroid tissue in the surgical specimen, 13 of these developed hypocalcemia and 13 remained normocalcemic. Of the 50 patients who developed hypocalcemia, 8 (15%) had 2 parathyroids in the specimen, and 42 (85%) had 1 parathyroid in the specimen. Of the 50 patients who did not develop hypocalcemia, 8 (15%) presented 2 parathyroid glands in the specimen and 42 (85%) had one parathyroid gland in the specimen.

Of the 24 symptomatic hypocalcemia patients, 17 had no parathyroids removed, 6 had one parathyroid removed and one had 2 parathyroids removed. Of the 26 asymptomatic hypocalcemia patients, 20 had no parathyroids removed, 5 had one parathyroid removed and one had 2 parathyroids removed. From these data, hypocalcemia appeared independent from parathyroid tissue in the specimen.

It was found that the greatest decrease in post-operative serum calcium levels, compared to pre-operative levels, occurred on the morning of the first post-operative day (12-18 hours after the operation). We, therefore, evaluated, for each patient, the difference (Δ) between pre-operative serum calcium and the level on the first post-operative assessment (usually the morning of the first post-operative day). Thereafter, an attempt was made to identify a threshold value of Δ which would best separate patients who became hypocalcemic from those who did not. First of all, the mean value was investigated of Δ (1.4 mg/dl) as possible cut-off (Table III). Using Fisher's exact test, patients with $\Delta \geq 1.4$ mg/dl were significantly more likely ($p < 0.0001$) to develop hypocalcemia than those with $\Delta < 1.4$ mg/dl. Nevertheless, 11 patients with $\Delta < 1.4$ mg/dl developed hypocalcemia. To reduce this number (i.e., increase sensitivity at the cost of reducing specificity) it was decided to lower the cut-off for Δ to the arbitrary value of 1.1 mg/dl, when only 8 patients below this cut-off developed hypocalcemia (Table IV). With the new threshold, patients with $\Delta \geq 1.1$ mg/dl were still significantly more likely ($p < 0.0001$) to develop hypocalcemia than those with $\Delta < 1.1$ mg/dl. In fact, of the 50 patients who developed hypocalcemia, 42 (84%) presented a decrease (Δ) of ≥ 1.1 mg/dl. And of the 50 patients who did not develop hypocalcemia, 23 (46%) presented a decrease of ≥ 1.1 mg/dl and 27 (54%) a decrease of < 1.1 mg/dl (Table III).

New post-operative monitoring protocol

A threshold of 1.1 mg/dl was adopted and a new protocol was elaborated for the management of post-operative hypocalcemia which was designed to reduce symptomatic

Table III. Distribution of hypocalcemia and normocalcemia in retrospective series of patients undergoing total thyroidectomy, according to the cut-off adopted for fall in post-operative blood calcium.

Cut-off mg/dl		Hypocalcemic* patients n = 50	Normocalcemic** patients n = 50	Total
1.4	$\Delta \geq 1.4$	39 (78.0%)	12 (24.0%)	51
	$\Delta < 1.4$	11 (22.0%)	38 (76.0%)	49
1.1	$\Delta \geq 1.1$	42 (84.0%)	23 (46.0%)	65
	$\Delta < 1.1$	8 (16.0%)	27 (54.0%)	35

*Hypocalcemia defined as < 8.0 mg/dl; ** normocalcemia defined as ≥ 8.0 mg/dl.

Table IV. Protocol proposed for prospective treatment of post-operative hypocalcemia in patients undergoing total thyroidectomy.

- Measure pre-operative serum calcium (mg/dl).
- Measure post-operative serum calcium (mg/dl) on morning of first post-operative day.
- Calculate Δ as latest pre-operative serum calcium minus first post-operative serum calcium.
- If $\Delta \geq 1.1$ mg/dl (reduction $\geq 12\%$ compared to pre-operative level) give calcium gluconate i.v., and supplement orally with calcium and vitamin D twice a day. Measure serum calcium on morning of second post-operative day; if within normal range, reduce by 50% the Ca dose; if low, continue with oral Ca and Vitamin D; if patient becomes symptomatic add calcium gluconate i.v. If $\Delta < 1.1$ mg/dl (reduction of $< 12\%$ compared to pre-operative level) no treatment but measure serum calcium on morning of second post-operative day (and if hypocalcemic start treatment).
- Measure serum calcium on morning of third post-operative day. If hypocalcemic, start treatment; if normocalcemic, discharge immediately after removal of drainage (third post-operative day).
- Measure serum calcium 24 hours after discharge (laboratory near patient's home). If hypocalcemic, patient instructed to contact attending physician by telephone.

hypocalcemia and also reduce hospitalization time. The protocol is shown in Table IV.

Prospective series

Enrolled in the prospective study, were 93 patients, however only 67 were evaluable as pre-operative calcium levels were not determined in 33. Of the 55/67 patients who developed hypocalcemia, 42/55 (76%) had $\Delta \geq 1.1$ mg/dl; of the 12/67 patients who remained normocalcemic 9/12 (75%) had $\Delta < 1.1$ mg/dl (Table V). The difference in hypocalcemia incidence between the two groups, defined by the 1.1 mg/dl cut-off, was significant ($p = 0.0013$; Fisher's exact test).

Application of the protocol (Table IV) was associated with a mean hospital stay of 4.73 (SD 0.18) days, including the day prior to surgery. The difference in duration of hospital stay, between the retrospective and prospective series, was significant ($p < 0.0001$, Student *t* test). The mean number of serum calcium measurements per patient

Table V. Distribution of hypocalcemia and normocalcemia in prospective series of patients undergoing total thyroidectomy according to groups defined by cut-off 1.1 mg/dl for decrease in serum calcium levels.

Δ (mg/dl)	Hypocalcemic patients* (n = 55)	Normocalcemic patients** (n = 12)	Total
≥ 1.1 mg/dl	42/55 (76.4%)	3/12 (25.0%)	45
< 1.1 (mg/dl)	13/55 (23.6%)	9/12 (75.0%)	22

*Hypocalcemia defined as < 8.8 mg/dl; **normocalcemia defined as ≥ 8.8 mg/dl.

was reduced from 13 in the retrospective series to 4 in the prospective series (77% reduction).

Discussion

The aim of the present study was not to investigate the causes of hypocalcemia following total thyroidectomy but to identify, at an early stage, patients at high risk of developing post-operative hypocalcemia, in order to start treatment and thereby avoid the clinical manifestations of the condition and permit a reduction in hospitalization time. For this reason, we did not select patients for age, sex, or type of thyroid disease and did not consider whether or not lateral or central neck dissection was performed.

There is considerable controversy concerning which measurements to perform – and when – to predict transient or permanent post-operative hypoparathyroidism. Some Authors recommend intra-operative and peri-operative iPTH monitoring^{7,9,12}. Asari et al. measured iPTH levels, 24 hours after total thyroidectomy, and calcium levels, on the second post-operative day, and found that with these measurements it was possible to predict hypoparathyroidism with high sensitivity, specificity and positive predictive value¹³. However, in another study, no significant correlation was found between PTH levels 24 hours after surgery and the development of significant hypocalcemia⁸. Yet another study supported the usefulness of iPTH monitoring, but noted that the high cost of monitoring represented a major limitation to clinical use³. Serum calcium may be monitored instead of PTH. Some centres repeat serum calcium measurements for several days until a rising trend is observed^{10,14}; others discharge patients early on calcium replacement without prolonged calcium monitoring². Nahas et al.¹⁰ recommended an algorithm involving calcium measurements, 6 and 12 hours post-operatively, to identify patients at risk of developing hypocalcemia.

From our retrospective evaluation of 100 patients, it was found that a maximum of 36 hours (morning of second post-operative day) was necessary to observe a decrease in serum calcium levels close to those expected to cause symptoms. More importantly, a marked decrease in serum calcium compared to pre-operative levels on the first post-operative measurement (morning of first post-operative day) was a reliable predictor of subsequent hypocalcemia.

We therefore studied the drop (Δ) in serum calcium between the last pre-operative assessment and that on the morning after surgery, and, after examining the distribution of Δ (Table III) adopted a 1.1 mg/dl (12% of pre-operative) as cut-off for predicting hypocalcemia and elaborated a protocol in which calcium replacement was started immediately if the fall was ≥ 1.1 mg/dl. An important aspect of this protocol was that patients were discharged as soon as drainage was removed (usually the third day) if serum calcium was in the range 8.8-10.2 mg/dl.

Choice of the 1.1 mg/dl cut-off derived from our experience in the prospective series: 42/55 hypocalcemic patients had $\Delta \geq 1.1$ mg/dl and 9/12 patients who did not develop post-operative hypocalcemia had $\Delta < 1.1$ mg/dl. The difference in hypocalcemia was significant ($p = 0.0013$, Fisher's exact test). Application of the protocol to our prospective series resulted in a reduced number of calcium measurements (from a mean of 13/patient in the retrospective series to a mean of 3/patient in the prospective series (at a cost 12 euro per test) and most importantly reduced hospitalization time from 6.2 days to 4.7 days with a consequent cost reduction of approximately 1000 euro/patient (hospitalization cost 500 euro/day). The proportion of patients who developed symptomatic hypocalcemia dropped only slightly from the retrospective (24%) to the prospective (19.4%) series (Table I). The increase in the proportion of hypocalcemic patients, from 50% in the retrospective series to 82% in the prospective series (Table I) is almost certainly due to the change in the definition of hypocalcemia by the analytical laboratory (increased from < 8.0 to < 8.8 mg/dl).

In conclusion, we propose herewith assessment of the drop in calcium levels post-operatively compared to the immediate pre-operative levels as a useful and simple predictor of hypocalcemia in patients undergoing total thyroidectomy. Adoption of 1.1 mg/dl (12% of pre-operative level) as cut-off for determining whether to start prophylactic calcium replacement, made it possible to discharge patients, on average, about 2 days earlier with a significant saving in costs.

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