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Hypocalcemia following total thyroidectomy: early factors predicting long-term outcome

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SUMMARY: Hypocalcemia following total thyroidectomy: early factors predicting long-term outcome.

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Hypocalcemia following total thyroidectomy (TT) must be considered permanent in patients requiring calcium replacement therapy after one year. The aim of this study was to identify early risk factors predicting long-term outcome of postoperative hypocalcemia. Among 453 patients who underwent TT from January 1998 to May 2003, a cross-sectional study between 44 patients with transient hypocalcemia (9,7%) and 3 patients with permanent hypocalcemia (0,7%) was carried out.

Both low serum calcium level (< 8 mg/dl) and high serum phosphorus level (>4,5 mg/dl), measured on postoperative day 7, were predictive for outcome. Central neck lymph node dissection, performed for thyroid carcinoma, also correlated with outcome. Serum phosphorus level >4,5 mg/dl on postoperative day 7 resulted the only independent factor predicting permanent hypoparathyroidism.

Therefore indication for central dissection would be very strict. When serum phosphorus level is unfavorable a correct replacement therapy is mandatory to prevent the consequences of permanent hypocalcemia.

RIASSUNTO: Ipocalcemia dopo tiroidectomia toale: fattori precoci predittivi dell'esito tardivo .

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L'ipocalcemia dopo tiroidectomia totale (TT) deve essere considerata permanente nei pazienti che richiedono terapia sostitutiva con calcio un anno dopo l'intervento chirurgico. Lo scopo di questo studio è stato di identificare i fattori di rischio precoci predittivi dell'esito tardivo dell'ipocalcemia postoperatoria. Dal gennaio 1998 al maggio 2003, 453 pazienti sono stati sottoposti a TT nel nostro Dipartimento. È stato condotto uno studio comparativo tra 44 pazienti con ipocalcemia transitoria (9,7%) e 3 pazienti con ipocalcemia permanente (0,7%).

Sia i bassi livelli postoperatori di calcio (< 8 mg/dl) sia gli alti livelli di fosforo (> 4.5 mg/dl) in settima giornata post-operatoria sono risultati predittivi dei risultati a distanza. Anche la linfettomia centrale eseguita per carcinoma tiroideo differenziato è risultata correlata con l'ipocalcemia permanente. Una fosforemia > 4.5 mg/dl in settima giornata postoperatoria è risultato essere l'unico fattore indipendente predittivo di ipoparatiroidismo permanente.

Le indicazioni alla linfettomia centrale dovrebbero essere perciò strettamente selezionate. Quando i livelli post-operatori del fosforo non sono soddisfacenti, la somministrazione della corretta terapia sostitutiva con calcio è obbligatoria per prevenire le conseguenze dell'ipocalcemia permanente.

KEY WORDS: Hypocalcemia - Permanent hypoparathyroidism - Total thyroidectomy.
Ipocalcemia - Ipoparatiroidismo permanente - Tiroidectomia totale.

Introduction

Hypocalcemia is often observed after total thyroidectomy. The incidence of postoperative hypocalcemia is reported ranging from 1.6% to 53.6% (2, 5, 13-17).

Hypoparathyroidism following thyroid surgery is the most important cause of chronic hypocalcemia, and it is strictly related to devascularization or involuntary removal of parathyroid glands. Hypocalcemia is more often transient and the parathyroid function

spontaneously recovers within few months from surgery. In patients requiring calcium replacement therapy after one year from the operation, hypoparathyroidism must be considered permanent (9-14). The risk of permanent hypoparathyroidism is reported varying from 0,5% to more than 8% (2-5, 13-17).

The aim of this study was to retrospectively assess the incidence of hypocalcemia following total thyroidectomy in our practice and to identify early risk factors predicting long-term outcome of hypocalcemia as hypoparathyroidism

Patients and methods

Patients who underwent total thyroidectomy in our Surgical Department from January 1998 to May 2003, with at least one

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TABLE 1 - PREDICTING FACTORS OF PERMANENT HYPOPARATHYROIDISM AFTER TOTAL THYROIDECTOMY.

| | <i>Transient hypocalcemia (Group 1)</i> | <i>Permanent hypocalcemia (Group 2)</i> | <i>p</i> |
|--|---|---|----------|
| Patients (n) | 44 | 3 | NA |
| Pathological diagnosis | | | |
| Carcinoma | 15 (34%) | 2 (66,6%) | 0.544 |
| Multinodular goiter | 22 (50,0%) | 1 (33,4%) | 1.000 |
| Toxic goiter | 7 (16,0%) | 0(0%) | 1.000 |
| Paresthesia on p.o. day 1 and 3 | 17 (38.6%) | 3 (100.0%) | 0.070 |
| Calcemia <8.0 mg/dl on p.o. day | | | |
| 1 | 35 of 44 (79.5%) | 3 of 3 (100.0%) | 1.000 |
| 3 | 16 of 44 (36.4%) | 3 of 3 (100.0%) | 0.060 |
| 7 | 2 of 44 (4.5%) | 2 of 3 (66.6%) | 0.016 |
| Phosphoremia >4.5 mg/dl on p.o. day | | | |
| 1 | 2 of 44 (4.5%) | 0 of 3 (0%) | 1.000 |
| 3 | 7 of 44 (15.9%) | 3 of 3 (100.0%) | 0.007 |
| 7 | 3 of 44 (6.8%) | 3 of 3 (100.0%) | 0.001 |

p.o. postoperative; NA, not applicable.

year follow up, were retrospectively evaluated to assess the incidence of postoperative hypocalcemia and permanent hypoparathyroidism. Serum calcium and phosphorus levels were daily measured after thyroidectomy with colorimetric method (Olympus System Reagent). The normal values of serum calcium with this technique were 8.10 mg/dl to 10.40 mg/dl, and 2.60 mg/dl to 4.50 mg/dl for the serum phosphorus level. Hypocalcemia was defined by serum calcium level <8.0 mg/dl and hyperphosphoremia by serum phosphorus level >4.5 mg/dl, as previous retained by other authors (14). In patients experiencing clinical symptoms or signs of hypocalcemia as paresthesia, intravenous or oral calcium and vitamin D3 supplementation was started. Patients were discharged with oral calcium and vitamin D3 prescription.

All patients with hypocalcemia were followed in our own or in the endocrinological outpatient Department, until serum calcium normalization without oral substitute. When both vitamin D3 and calcium administration was required one year after thyroidectomy, patient was retained as having permanent hypoparathyroidism. In this subgroup of patients, delayed levels of 1-84 parathyroid hormone (PTH) were detected. PTH levels were measured with immune radiometric assay (normal range 12-72 pg/ml).

We carried out a cross-sectional study to identify the early risk factors predicting long-term outcome of hypocalcemia. The characteristics of two groups of operated patients were compared: group 1 consisted of patients with restoration of eucalcemia and group 2 of patients with permanent hypoparathyroidism. Patients were well-matched for demographic data (sex and age), type of thyroid disease, different operative techniques, biochemical and clinical features. For the cross-sectional study between groups 1 and 2, the daily postoperative blood samples considered were those on postoperative day 1, 3 and 7.

Each surgical operation consisted of an extracapsular total thyroidectomy. In case of lymph node involvement by a thyroid differentiated carcinoma, central neck lymph node dissection or combined central and modified radical neck dissection was also performed. Our surgical policy was to identify and preserve all

parathyroid glands after identification of their vascular pedicles and very mild dissection by ultraligatures and bipolar coagulation. When a venous infarction of parathyroid was recognized, a small decompressing incision and hydration on the gland was made with careful checking of the end result. A compromised parathyroid gland was immediately autotransplanted in the homolateral sternocleidomastoid muscle.

Statistical univariate analysis of the cross-sectional study was performed using the Student's t-test, the chi-square test, and the Fischer's exact test when adequate. Differences were considered significant when $p < 0,05$. A multivariate analysis using the multiple regression test was made to determine the independent risk factors related to permanent hypoparathyroidism.

Results

Over the period from January 1998 to May 2003, 453 patients underwent total thyroidectomy in our Surgical Department for a variety of endocrine disorders. Forty seven patients experienced postoperative hypocalcemia (10,4%). Forty four patients had transient hypocalcemia (9,7%) and in three other patients, requiring calcium and vitamin D3 supplementation one year after total thyroidectomy, permanent hypoparathyroidism was considered (0,7%). In this subgroup of 3 patients, delayed mean PTH levels were less than 12 pg/dl. As a result of the cross-sectional study, group 1 consisted of 44 patients with transient hypocalcemia and group 2 of 3 patients with permanent hypocalcemia (Table 1). The two groups were homogenous for sex and age, patients of group 1 with mean age of 48,8 years (range 27-69 years) *versus* patients of group 2 with mean age of 44,6 years (range 29-60 years) ($p=0,494$).

TABLE 2 - PERMANENT HYPOCALCEMIA RELATED TO SURGICAL PROCEDURE ON 453 PATIENTS.

| <i>Surgical procedure</i> | <i>Total thyroidectomy (419 pts)</i> | <i>Central neck dissection (34 pts)</i> | <i>p</i> |
|---------------------------|--|---|----------|
| Transient hypocalcemia | 37 | 7 | 0.054 |
| Permanent hypocalcemia | 1 | 2 | 0.005 |

Permanent hypocalcemia was not related to final pathological diagnosis. No significant difference was found about early clinical symptoms of hypocalcemia as paresthesia (Table 1). Three out of 47 patients underwent parathyroid autotransplantation without statistically valid conclusions.

Serum calcium and serum phosphorus levels measured on postoperative day 7 were predictive for long-term outcome by univariate analysis ($p=0,016$ and $p=0,001$; Table 1). Among 34 patients who underwent total thyroidectomy associated with central neck dissection, 9 patients experienced hypocalcemia (26,4%) and this surgical procedure was correlated with long-term outcome of hypocalcemia by univariate analysis ($p=0,005$; Table 2). Nevertheless, only serum phosphorus level above 4,5 mg/dl on postoperative day 7 resulted as early independent factor predictin long-term outcome of hypocalcemia by multiple regression tests analysis ($p=0,0004$).

Moreover, we report that there was no evidence of severe postoperative hypocalcemia in the last 120 operated patients.

Discussion

Hypocalcemia is a specific complication of neck surgery and particularly of total thyroidectomy. Although hypocalcemia recovers spontaneously in most cases, some patients require lifelong calcium and vitamin D3 replacement therapy (9-14).

In the current study, the Authors found an incidence of 9,7% of transient hypocalcemia and of 0,7% of permanent hypoparathyroidism following total thyroidectomy. A systematic review of the literature showed a well comparison between this result and analogous published reports, owing to incidences of postoperative hypocalcemia and permanent hypoparathyroidism ranging from 1,6% to 56,3% and 0,5% to 8,6%, respectively (2-5, 13-17). The dissimilar range of hypocalcemia reported in literature are due to different laboratory methods, to different cutoffs of hypocalcemia adopted by other authors, to particular thyroid diseases, and to different surgical technique. In this study, hypocalcemia was definend as serum calcium level under 8,0 mg/dl and hyperphosphoremia as serum phosphorus level above 4,5

mg/dl (14).

There are a number of minor reasons of hypocalcemia as postoperative hemodilution or low serum proteins concentration (6), but the most important cause is trauma or parathyroid devascularization during surgery (14). Thyroidectomy exposes the patient to the risk of this complication, as a result of close topographic relationship between thyroid and parathyroid glands. Moreover, the blood supply of parathyroid gland is guaranted by a little terminal artery originated from thyroid arteries (12). Our surgical policy was to identify and preserve all parathyroid glands, to decompress parathyroid venous infarction, or to immediately autotransplant a compromised parathyroid gland, which seems to guarantee good results on prevention of permanent hypoparathyroidism (13).

Chronic and irreversible effects of an unrecognized hypoparathyroidism can be summarized as follows: early cataracts; altered mental status and neurological effects from basal ganglia calcifications, such as parkinsonian symptoms; decreased cardiac contractility; muscles cramping and spasms; and ossification of the paravertebral ligaments (3-7).

The aforesaid considerations are of particular interest for the surgeon and motivate the search for predictive risk factors of hypoparathyroidism following thyroid surgery, in order to prevent the consequences of a mistreated hypoparathyroidism.

Although in our experience permanent hypocalcemia was not related to the final pathological diagnosis (Table 1), literature review demonstrates more frequent hypoparathyroidism in case of thyroidectomy performed for hyperthyroidism and thyroid cancer (10-11, 19).

The presence of clinical symptoms or signs of hypocalcemia as paresthesia didn't correlated with outcome of hypocalcemia (Table 1).

Despite oral calcium substitute, both low serum calcium level (<8 mg/dl) and high serum phosphorus level (>4,5 mg/dl) measured on postoperative day 7 were predictive for long-term outcome of hypocalcemia (Table 1). Nevertheless, serum phosphorus level above 4.5 mg/dl on postoperative day 7 resulted as the only risk factor predicting long-term outcome by multiple regression test analysis. On the other hand, delayed serum calcium above 8.0 mg/dl, and mainly

delayed phosphoremia under 4.5 mg/dl, may be considered as positive predictive value of recovering of parathyroid function (1-4, 8-14).

In accordance to other authors, central neck lymph node dissection performed in case of thyroid carcinoma correlated significantly with permanent hypoparathyroidism occurrence (Table 2) (9-10,18). When performing central neck dissection, it is technically difficult to preserve the blood supply of the two inferior parathyroids glands (9). After removal of two or more parathyroid glands, spontaneous recovery of parathyroid function is not easy (9). Sometimes a supernumerary parathyroid gland can compensate for the loss of function (14).

A surgical strategy aimed to identify and preserve all parathyroid glands during thyroidectomy is the

main way to contain permanent hypoparathyroidism within its nadir incidence. Following this rule, in the last 120 operated cases of our series there was no evidence of severe postoperative hypocalcemia.

The indication for lymph node dissection in the central neck area would be very strict, because this procedure may seriously compromise the blood supply of the inferior parathyroid glands (9). Finally, when delayed serum phosphorus level is unfavorable, such as phosphorus level above 4.5mg/dl on postoperative day 7, an adequate follow up is mandatory for the early identification of patients undergoing hypoparathyroidism and for administering lifelong replacement therapy with the aim of avoiding the complications of chronic hypocalcemia.

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