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Which therapy to prevent post-thyroidectomy hypocalcemia?

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SUMMARY: Which theraphy to prevent post-thyroidectomy hypocalcemia?

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Hypocalcemia is one of the most frequent complications after total extracapsular thyroidectomy (TET). In most of cases it is a transient phenomenon. The aim of this study is to evaluate if and how the oral administration of calcium or calcium combined with D-vitamin could effectively prevent post-thyroidectomy hypocalcemia.

A randomized prospective study was performed, recruiting 120 patients who underwent total thyroidectomy.The patients in our series were randomly assigned to one of two groups: group A - patients who received calcium lactogluconate/ calcium carbonate (mg 300 per day); group B - patients who received calcium carbonate/cholecalciferol therapy (calcium carbonate: 1500 mg per day; cholecalciferol 400 UI per day). The groups were well mateched for age, sex and pathologies. Patients of both A and B groups were divided in two subgroups: those operated on for benign thyroid diseases (A1 and B1) and those operated on for malignancy (A2, B2).

Serum calcium assays, performed 24, 48 and 72 hours after surgery, showed mean values of calcemia higher in patients of the B1 and B2 group. Statistical analysis was performed using a Student's t test. Mean serum calcium concentrations on post-operative day one, two and three were higher in patients of the group B ($p<<0.01$).

Early and combined oral administration of both calcium and vitamin D seemed to prove major efficacy in preventing and treating post-operative hypocalcemia, showing mean serum calcium levels higher than those of patients who received only oral calcium administration. Nevertheless, further studies are necessary to validate these data.

RIASSUNTO: Quale terapia nella prevenzione dell'ipocalcemia post-tiroidectomia totale?

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L'ipocalcemia è una delle più frequenti complicanze dopo tiroidectomia totale. Scopo di questo studio è di valutare se e in che modo la somministrazione orale di calcio con vitamina D può prevenire l'ipocalcemia post-tiroidectomia.

È stato condotto uno studio prospettico randomizzato, reclutando 120 pazienti sottoposti a tiroidectomia totale. I pazienti studiati sono stati randomizzati in uno dei seguenti gruppi: gruppo A - pazienti a cui è stato somministrato ca gluconato / calcio carbonato (300 mg /die); gruppo B - pazienti a cui è stato somministrato calcio carbonato/colecalciferolo (calcio carbonato 1500 mg/die; colecalciferolo 400 UI / die). I gruppi erano omogenei per età, sesso e patologie. I pazienti di entrambi i gruppi sono stati divisi in due sottogruppi: quelli operati per tireopatie benigne (A1 e B1) e quelli operati per cancro (A2 e B2).

I dosaggi del calcio sierico praticati a 24, 48 e 72 ore dall'intervento hanno mostrato valori medi della calcemia più alti nei pazienti dei gruppi B1 e B2. L'analisi statistica è stata condotta utilizzando il test di Student. La calcemia in I, II e III giornata postoperatoria si è rivelata più alta nei pazienti del gruppo B ($p < 0,01$).

La somministrazione precoce e combinata di calcio e vitamina D è risultata più efficace nella prevenzione e nel trattamento dell'ipocalcemia post-operatoria, dal momento che i valori medi di calcemia sono risultati più alti di quelli dei pazienti a cui era stato somministrato soltanto calcio. Ulteriori studi sono comunque indispensabili per convalidare questi risultati.

KEY WORDS: Thyroidectomy - Hypocalcemia - Hypoparathyroidism - D-vitamin - Calcium.

Introduction

Hypocalcemia is one of the most frequent complications after total extracapsular thyroidectomy (TET). It can occurr from two to five days after surgery and requires post-operative supplementataion of calcium to prevent and treat symptoms. In most of cases it is a transient hypocalcemia whose incidence varies from 2 to 53% in literature (1-18), while permanent hypocalcemia (requiring calcium replacement therapy after one year) accounts for about 0,4-13,8% (19).

The aim of this study is to evaluate if and how the

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oral administration of calcium or calcium combined with D-vitamin could effectively prevent post-thyroidectomy hypocalcemia.

Patients and methods

A randomized prospective study was performed from October 2003 up to April 2005, recruiting 120 patients who underwent total thyroidectomy in order to determine the incidence of post-operative hypocalcemia. The principal exclusion criteria were hypercalcemia and chronic kidney failure.

On the basis of the oral calcium therapy administrated, the patients in our series were randomly assigned to one of two groups:

- group A - patients who received calcium lactogluconate/calcium carbonate (mg 300 per day);
- group B - patients who received calcium carbonate /cholecalciferol therapy (calcium carbonate: 1500 mg per day; colecalciferol 400 UI per day).

The two groups were well-matched for number, age, sex of patients. Group A included 60 patients (28 males, 32 females; mean age: 36,8 years old), all but 7 suffered from benign thyroid disease; 7 patients suffered from thyroid malignancies (except C cells tumours). Group B also included 60 patients (25 males and 35 females, mean age: 47,8 years old); also in this group 7 patients were operated on for thyroid malignancies, all the others for benign thyroid pathologies. All the patients were euthyroid at the time of surgery. Those who were hyperthyroid before, received therapy until normalization of serum thyroid hormones.

All the patients started the therapy on the first post-operative day combining L-tiroxin (100 γ os per day). Serum calcium levels were measured 24, 48 e 72 hours after surgery. PTH was not measured. Symptoms as perioral tingling, muscle cramp, Chvostek's and Trousseau's signs were also checked and registered by nurses. If severe (defined as calcium concentrations of < 8 mg/dL) or symptomatic hypocalcemia occurred, patients received iv calcium gluconate administration (18,4 mEq). Patients were discharged in a mean of three days after surgery (if no complications occurred), and discontinued the oral therapy within 15 days after the operation.

Serum calcium was checked 30, 60, 90 and 120 days after surgery. If symptoms or signs of hypocalcemia lasted, the therapy was continued until stable normalization of serum calcium.

Data of the 4 groups were analyzed and compared. Statistical analysis was performed using a Student's t test. In all cases α was set on 0.01.

Results

Patients of both A and B groups were divided in two subgroups: those operated on for benign thyroid diseases (A1 and B1) and those operated on for malignancy (A2 and B2). Serum calcium assays, performed 24, 48 and 72 hours after surgery, showed mean values of calcemia of 8,4, 8,7 and 8,6 mg/dL (group A1); 9,1, 9,3 and 9,3 mg/dL (group B1); 8,3, 8,2 and 8,4 mg/dL (group A2); 9, 8,7 and 9,4 mg/dL (group B2). The SD were similar in all groups.

Mean serum calcium concentrations on post-operative day one, two and three were higher in patients of the group B ($p<0.01$), furthermore ANOVA measures showed that the patients of the group B1 and B2 had higher mean serum calcium concentrations on post-operative day one, two and three ($p<0.01$) (Figs. 1 and 2). A different trend in the post-operative serum calcium was also observed in patients of the B1 and B2 groups, that is, those who underwent surgery for malignancies of the thyroid, as discussed beyond (Fig. 2).

Four patients (6,6%) among the A group and 1 of the group B (1,6%) experienced symptomatic hypocalcemia, which required intravenous administration of calcium gluconate (18,4 mEq iv). The patients lamented muscle cramps and tingling. The only adverse effect recorded among patients of the B group was mild gastric pirosis, mostly in long-lasting therapies.

Discussion

Hypocalcemia (defined as serum calcium < 8.0 mg/dL) is a common event after extensive thyroid surgery. Some Authors in literature report an incidence of about 75% (20) of such complication. In most of cases it is a transient phenomenon, not caused by permanent hypoparathyroidism, but due to transient parathyroid "stupor" (2, 3, 5-7, 10, 11, 13, 14, 19, 20).

Several hypotheses have been enunciated to explain the phenomenon (1-3, 6-8, 10-14, 19, 20, 22), whose incidence - it has to be stressed - is higher in patients who undergo TET (12). Among the others, unintentional ablation of parathyroids, or their ischemic damage - either as temporary ischemia (8, 17, 20), either as the effect of bilateral truncal ligation of the inferior thyroid artery or parathyroid artery (hypothesis rejected by some Authors 9) - and hypoalbuminemia (6, 8, 20) resulting from surgical stress and hemodilution (10) must be cited. A temporary parathyroid insufficiency and the avidity of the skeleton for calcium in hyperthyroid patients may also aggravate the hypocalcemia (10, 21).

Thus, the pathogenesis of early hypocalcemia is multifactorial and yet unknown. As previously mentioned, hypoparathyroidism due to the incidental resection of parathyroid glands is an exceptional event (3), since it would be caused by the simultaneous resection of the four parathyroid glands and would show permanent features. The incidence of permanent hypocalcemia (about 6% in the Authors' personal experience and from 0,4 to 13% in literature) (2-5, 8, 10, 12, 15, 20, 22) is low, so as the rare event of the simultaneous resection of the four parathyroids - either for the surgeon's intraoperative ability of recognition and his/her technical skill (15), either for the frequent abnormalities of number and site of the glands .

Some of the Authors (3) showed in a previous

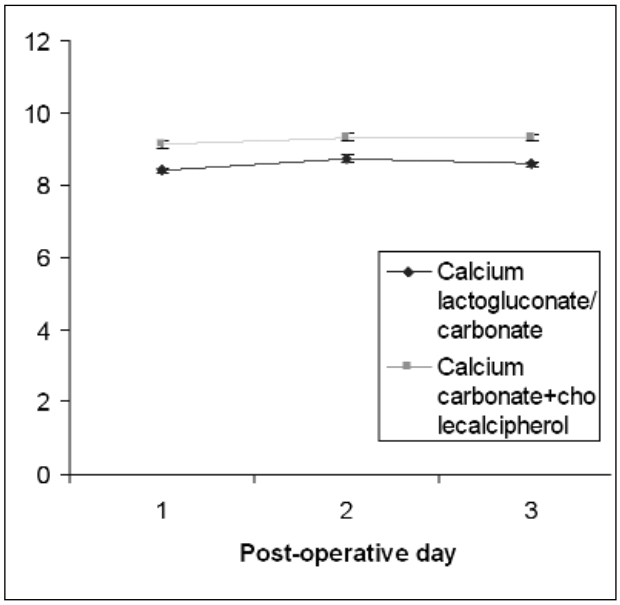

Fig. 1 - Serum calcemia in pts. operated on for benign thyroid diseases.

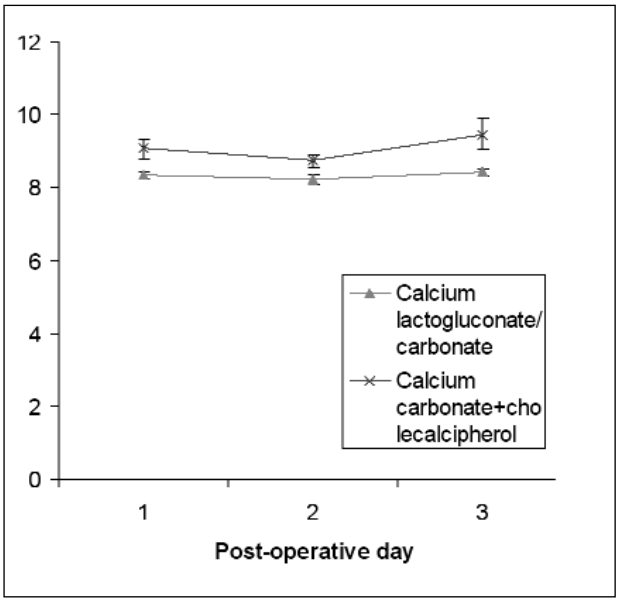

Fig. 2- Serum calcemia in pts. operated on for malignant thyroid diseases.

report that the incidence of post-operative hypocalcemia was higher in patients with mediastinal immersion of the goiter (15%) in patients suffering from autoimmune diseases (33%) and cancer (5%). Hypocalcemia also seemed to be long-lasting or permanent in case of hyperfunction (6,25%) and recurrence (6,25%)(3). Some Authors in literature showed a trend of hypoparathyroidism to be more frequent in patients operated on for Graves' disease and thyroid cancer than in other thyroid disorders (4,11). Untreated hyperthyroidism, could be responsible for a higher need for calcium afer surgery, because of the increased bone reconstruction (the so-called "hungry bone syndrome"). This is a complication to be afraid of in cases of severe, prolonged hypertyroidism (21).

All the patients in our series were euthyroid at the time of surgery (previous treatment in case of hyperfunctioning thyroid disease).

Others (12, 14,17) observed an increased incidence of permanent hypocalcemia in patients who underwent total thyroidectomy, repeat thyroidectomy, thyroidectomy plus neck dissection, whereas lobectomy or subtotal thyroidectomy for benign euthyroid disease were low risk operations.

In our Department the post-operative standard therapy also provides early administration (since the first post-operative day) of L-tiroxin (100 γ/die os) since, has reported elsewhere (3), we are firmly persuaded that the thyroid hormones deficiency is one of the factors causing hypocalcemia and, thus, it should be prevented.

Seldom patients present clear symptoms of hypocalcemia, such as tingling sensation, muscle cramps, laryngeal spasm (at times lethal) and the typical Chvostek's and Trousseau's signs. More frequently patients experience peripheral tingling and perioral numbness. Also anxiety and/or depression can occurr, mostly in long-lasting hypocalcemia. Lastly, in some cases, hypocalcemia can be just an asymptomatic laboratory finding (17).

Usually the lowest serum calcium level is seen 48-72 hours after surgery and returns to normal in seven days after surgery (5). Symptoms usually occurr 24 to 48 hours after the operation (22). Some Authors (5) showed that the critical period for monitoring of serum calcium was 24 to 96 hours after surgery; and if serum calcium replacement was not needed in the first 72 hours after surgery, it would not seldom be needed thereafter (5). That is why in our series serum calcium was monitored 24, 48 and 72 hours after surgery. We did not measure serum PTH since we did not consider hypoparathyroidism to be the only factor causing hypocalcemia.

In all the cases, we started the early administration of L-tiroxin, calcium and D-vitamin (first post operative day), getting not only the calcium benefit, but also the one of D-vitamin which plays a key role in the absorbtion and the excretion of calcium (23); it also seems to act directly on cellular membranes causing the sudden increase of intracellular calcium, thanks to little variations of the cellular membrane. Calcium carbonate is absorbed by the duodenum and 20 to 30% of such mechanism is a D-vitamin dependent transfer (23). Low-phosphate diet should also be recommended.

The patients of the B Group (calcium + vitamin D administration) in our series showed (respectively

on first, second and third postoperative day) mean calcium values of 0,7 0,6 and 0,7 mg/dL higher than patients of the A group (only calcium administration). This was a statistically significant difference ($p<0.001$).

As shown in Figure 1, serum calcium shows an increase on the second post-operative day and then a slight decrease on the third post-operative day in patients operated on for benign diseases. A clear explanation of this calcium trend is yet not clear, but is already reported by other Authors in literature (13). Patients of the B group also showed fewer symptoms than patients in the A group (respectively 1,6% vs. 6,6%).

It is also interesting to note that the multivariate analysis of data concerning TET for malignancies showed a different trend in calcium behaviour: in these cases, in fact, patients of both A and B group experienced a decrease of mean calcium values on the second post-operative (p.o.) day, that increased on the third p.o. day but showed mean values lower than those of patients of both groups operated on for benign diseases (Fig. 2). This trend could be due to the wider excisions performed in case of malignancy with subsequent major parathyroid (transient or permanent) damage.

The only argument in contrast with combined vitamin D-calcium therapy (that is that both they could inhibit PTH secretion by normally functioning parathyroid glands) has been refuted by some Authors in literature. (23). In addition, others (19) stated that delayed serum calcium and phosphorus levels, measured one week after starting calcium therapy, could preview the outcome of hypocalcemia after thyroidectomy, but the administration of any vitamin D analogs would interfere with such predictability.

The only adverse effect recorded in patients of the B group was gastric pirosis.It could be related to the the sorbitol in the clinical formula. No signs or symptoms of vitamin D intoxication were observed.

Conclusions

Post-thyroidectomy (and, more extensively, post-operative) hypocalcemia is a frequent and multifactorial event (1-23). In most of cases it is a transient phenomenon. In our experience it seems to reach the lowest values in patients who undergo TET for malignant diseases, especially on the second post-operative day.

Furthermore, early and combined oral administration of both calcium and vitamin D seemed to prove major efficacy in preventing and treating post-operative hypocalcemia, showing mean serum calcium levels higher than those of patients who received only oral calcium administration.

Thus, further studies are necessary to validate these data, and the review of data in literature suggest new perspectives of investigation concerning the evaluation of the efficacy of the oral administraton of combined calcium and vitamin D starting from the day before surgery in order to prevent post-thyroidectomy hypocalcemia, so as the use of thiazid diuretics to avoid hypercalciuria (18).

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