WHAT SHOULD BE THE APPROACH TO MODERATE HYPOCALCAEMIA IN THE EARLY PERIOD FOLLOWING TOTAL THYROIDECTOMY?

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Abstract

Context. It is unclear whether treatment is necessary for transient moderate hypocalcaemia occurring after total thyroidectomy; if it is present, it is unclear which treatment modality should be preferred.

Objective. To investigate both the necessity and effectiveness of different treatment approaches of oral and/or intravenous calcium treatment in patients with transient, postoperative, moderate hypocalcaemia.

Design. This is a case control study made between June 2014 and June 2015.

Subjects and Methods. Forty-five patients who had serum calcium levels 6 hours after total thyroidectomy between 7.5-8 mg/dL were divided into three equal groups: an oral calcium administration group, an intravenous calcium administration group and a no-treatment group. Serum calcium and parathyroid hormone levels were measured preoperatively and on postoperative days 1, 2, 5 and 10.

Results. For post-thyroidectomy patients with serum calcium 7.5-8 mg/dL in the early postoperative period, no significant difference in serum calcium or parathyroid hormone was detected between groups.

Conclusions. Follow-up without treatment seems to be the most effective approach for moderate hypocalcaemia occurring in the early period following total thyroidectomy; this suggests that intravenous treatment should be avoided.

Key words: Thyroidectomy, Hypocalcaemia, Parathyroid hormone, Calcium, Treatment.

as direct damage, ischemia and accidental excision of parathyroid tissue during surgery are the most common causes of transient or permanent HP. In 10% of the patients, transient HP (less than 6 months) occurs following thyroid surgeries, and in about half of these patients, permanent (at more than 6 months) HP develops (3-5).

Whereas HP-related hypocalcaemia might progress asymptotically in patients with slightly decreased calcium levels, in the case of a severe drop in calcium level, symptoms such as the development of muscle spasms and paraesthesia can arise (6). In the literature, there is no agreement on the issue of management of hypocalcaemia occurring in the early period following thyroidectomy. Whereas some authors recommend routine calcium and vitamin D supplementation to decrease the severity and incidence of hypocalcaemia after thyroidectomy (8, 9), some authors believe that this approach is unnecessary and even harmful, and treatment should be organized according to particular parameters, most importantly serum calcium and parathyroid hormone (PTH) levels (10). However, there is insufficient evidence regarding the mode of treatment or whether the treatment should be given. In this study, we aimed to investigate both the necessity and effectiveness of different treatment approaches by dividing patients who had calcium levels at postoperative hour 6 between 7.5 and 8 mg/dL (in other words, patients with moderate hypocalcaemia) into three groups.

INTRODUCTION

Hypoparathyroidism (HP)-related hypocalcaemia is the most common complication following total thyroidectomy and prolongs the duration of hospital stay (1). Recently, an increase in the frequency of thyroid cancers has led to more frequent total thyroidectomies and neck dissections and, in turn, an increase in the frequency of HP (2). Situations such

PATIENT AND METHODS

Consent for the study protocol was given by Local Ethics Committee. Written informed consent was obtained from all patients involved in the project. This study comprised 178 patients who were admitted to the “Bezmialem” University Endocrine Surgery

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Department between June 2014 and June 2015 for total thyroidectomy. The inclusion criteria for the patients were: serum calcium levels at postoperative hour 6 were between 7.5 and 8.0, age > 18 years old, euthyroid, normoparathyroid condition, a total thyroidectomy without any additional surgical procedures was performed for the first time. The exclusion criteria were the following: serum calcium level at postoperative hour 6 below 7.5 mg/dL or above 8.0 mg/dL, American Society of Anesthesiology (ASA) score 4, age < 18 years old, history of neck surgery, recurrent thyroid disease, additional surgical procedures along with total thyroidectomy (central or lateral neck dissection, simultaneous excision of parathyroid adenoma, etc.), concomitant parathyroid disease, hyperparathyroidism or hypercalcemia and refusal to participate in the study. Forty-five patients who met the inclusion criteria (9 male, 36 female, average age: 39.8 years, range: 18-60) were enrolled in the study. The patients were randomized to one of three groups. Group one was the oral calcium group, group two was the intravenous (IV) calcium group and group three was the control group. Patients in the first group were administered an oral calcium preparation containing 1200 mg/day ionized calcium (Calcium Sandoz efervesan tablet®, Eczacıbasi Co, Istanbul, Turkey). Patients in the second group were administered an IV calcium preparation containing 225 mg calcium gluconate + 572 mg calcium levulinate (Calcium Picken %10 ampul®, Adeka,

Istanbul, Turkey). No treatment was administered to patients in the third group. However, in case of development of hypocalcaemia symptoms (Chvostek's sign and/or Trousseau's sign and/or muscle spasms) during follow-up of all patients, supplementation with intravenous calcium was given. For all patients, total thyroidectomies were performed by two general surgeons who were experienced in endocrine surgery, and the parathyroid tissues of all patients were observed preoperatively and preserved. Following the surgery, the extracted specimens were sent for pathological examination to determine whether parathyroid tissue was present in the pathological specimen. The serum calcium and parathyroid hormone levels of all patients were measured preoperatively, at postoperative hour 6, and on postoperative days 1, 2, 5 and 10. At the time of discharge, patients were evaluated for hypocalcaemia and its symptoms, and at each follow-up visit patients were evaluated for Chvostek's sign, Trousseau's sign and muscle spasms. The clinical and laboratory parameters, which were obtained along with the demographical features of the patients, were recorded and compared among groups.

RESULTS

For post-thyroidectomy patients with serum calcium 7.5-8 mg/dL in the early postoperative period, no significant difference in serum calcium or PTH was

Table 1. Distribution of patients with serum calcium levels between 7.5 and 8 mg/dL according to treatment group

Groups	Preoperative (n)	Postoperative Hour 6 (n)	Postoperative Day 1 (n)	Postoperative Day 2 (n)	Postoperative Day 5 (n)	Postoperative Day 10 (n)
1	0	15	14	10	6	4
2	0	15	14	9	5	3
3	0	15	15	11	6	5

Legend: Group 1= oral supplementation, Group 2 = iv supplementation, Group 3= no treatment.

Table 2. Average calcium levels according to patient groups

Groups	Preoperative (mg/dL)	Postoperative Hour 6 (mg/dL)	Postoperative Day 1 (mg/dL)	Postoperative Day 2 (mg/dL)	Postoperative Day 5 (mg/dL)	Postoperative Day 10 (mg/dL)
1	9.23±0.22	7.79±0.12	7.81±0.21	8.04±0.5	8.37±0.63	8.7±0.7
2	8.98±0.25	7.68±0.2	7.91±0.28	7.98±0.42	8.55±0.79	8.46±1.69
3	9.04±0.24	7.81±0.18	7.76±0.14	7.92±0.39	8.39±0.66	8.53±0.6

Legend: Group 1= oral supplementation, Group 2 = iv supplementation, Group 3= no treatment.

Table 3. Preoperative and postoperative average PTH levels of patients

Groups	Preoperative (µg/dL)	Postoperative Hour 6 (µg/dL)	Postoperative Day 1 (µg/dL)	Postoperative Day 2 (µg/dL)	Postoperative Day 5 (µg/dL)	Postoperative Day 10 (µg/dL)
1	72.7±14.1	38.2±19.6	35.9±21.3	38.2±18.3	35.4±22.7	40.8±23.8
2	79.1±17.8	39.3±28.4	34.4±22.8	30.6±23.4	38.4±19.4	43.3±16.5
3	66.4±20.3	46.8±23.2	36.1±24.6	34.8±20.4	28.5±18.1	39.4±17.9

Legend: Group 1= oral supplementation, Group 2 = iv supplementation, Group 3= no treatment.

detected among patients administered oral calcium, IV calcium, and no calcium (Table 1). The results showed that preoperative serum PTH and calcium levels decreased significantly during the postoperative period, but no significant difference in either PTH or calcium level was detected among groups during the postoperative follow-up period (Tables 2, 3). Chvostek's and/or Trousseau's signs were observed on the second day of follow-up of one patient who was administered oral calcium, as well as on the second and third days of follow-up of two patients who were administered IV calcium. For each of the three patients, 900 mg IV calcium in 100 mL of 0.9% saline was additionally administered for one dose. No further problem occurred for these three patients during subsequent follow-up. Parathyroid tissue was not detected in the examination of pathological specimens for any of the cases.

DISCUSSION

For early diagnosis of hypocalcaemia following total thyroidectomy, serum PTH levels are checked, and it has been suggested that a decrease in PTH concentration within a couple of postoperative hours might be useful in the early detection of hypocalcaemia. Lombardi *et al.* recommended measuring intact PTH once within a couple of hours after thyroidectomy for patients at risk of hypocalcaemia and for whom an early discharge is planned (7). Lam *et al.* suggested that if the PTH level measured a couple of hours after thyroidectomy is less than 8 pg/mL, hypocalcaemia might clinically develop (11).

On the other hand, some publications suggest that measuring PTH is not sufficient for predicting and revealing postoperative hypocalcemia and, hence, it is not sufficient for predicting the clinical symptoms of hypocalcaemia (12-14). In an article evaluating four Australian studies that investigated the role of PTH in predicting postoperative hypocalcaemia, the sensitivity, specificity and positive predictive values of PTH following thyroidectomy in 458 patients were found to be 70.7%, 92.6% and 71.6%, respectively (12). A new treatment algorithm was applied following total thyroidectomy, and PTH and calcium levels were checked at postoperative hour 1. In 21% of patients, although PTH levels were low, hypocalcaemia was not observed (13). In another study, the PTH levels of 230 post-thyroidectomy patients at postoperative hour 4 were compared with the calcium levels on postoperative day 1, and whereas hypocalcaemia was

observed biochemically in 18 of 59 (30.5%) patients with PTH levels below 10 pg/mL; major symptoms developed in only one of these patients (14).

Due to the unreliability inherent in this contradiction involving PTH levels, some authors defend the necessity of administering oral calcium and vitamin D to all patients during discharge in order to safely provide early discharge and to prevent symptoms of hypocalcaemia following thyroidectomy (9, 15, 16). However, Delbridge *et al.* reported that 12% of patients who were routinely administered calcium and vitamin D following thyroidectomy were re-admitted to the hospital due to hypercalcemia (17). Other authors have reported that selection of patients and treatment according to this are necessary (10, 14, 18).

In a study conducted by Landry *et al.* of 156 patients who underwent thyroidectomy due to malignant and benign causes, calcium and PTH levels were evaluated, and patients were divided into two groups. Patients who developed hypocalcaemia during the postoperative period, patients with PTH levels below 3 pg/mL on postoperative day 1 and patients with calcium below 7 mg/dL on postoperative day 1 were included in the first group (n = 34), and the remaining patients were included in the second group (n = 122). They recommended beginning oral calcium and/or calcitriol supplementation during discharge for those patients with PTH levels below 6 pg/mL and/or calcium levels below 8 mg/dL, and they reported that unnecessary treatment might thus be prevented in 58% of the patients by providing calcium supplementation during discharge of all thyroidectomy patients (10).

A study conducted by Pasquale *et al.* compared the preoperative and postoperative serum calcium and PTH levels of 995 patients who underwent total thyroidectomy and observed the symptoms that developed postoperatively; oral and/or IV calcium treatment was administered according to calcium levels and patient symptoms, and they suggested that oral calcium supplementation is necessary and should be started for patients with a postoperative PTH level decrease of more than 70% and a serum calcium level decrease of more than 12% (18).

The issue of managing hypocalcaemia that develops in early period following thyroidectomy remains controversial. We believe that two points are significant in the path to resolving this issue. One point is determination of the severity of hypocalcaemia (severe or moderate), and the other point is determination of an approach to treatment for cases with a treatment indication. In our literature review, we

did not encounter a randomized study that addressed the first point by classifying hypocalcaemic patients as severe and moderate. In fact, a consensus concerning the treatment of severe and/or acute hypocalcaemia and relieving the symptoms of the patients by an oral or, if necessary, IV route according to the severity seems to have been reached (19). However, the main problems are whether treatment should be given to patients with moderate hypocalcaemia that develops in the early period following thyroidectomy and if so, which route is preferable, in the presumption that a transient hypoparathyroidism develops in some cases (20). Therefore, we based our study on patients with serum calcium levels of 7.5-8 mg/dL, which we accepted as moderate hypocalcaemia. During the postoperative follow-up, when the status of moderately hypocalcaemia was revealed, the serum calcium and PTH levels of patients from the oral, IV and no-treatment groups were compared, and we observed no significant difference among groups. This study yielded two major results: one is that subjecting patients to the invasiveness and potential risk for complication of IV treatment might be unnecessary because we did not observe any difference between the effectiveness of the oral or IV approach for patients with moderate hypocalcaemia that developed in the early period following total thyroidectomy. The second and more important result is that these patients can be followed-up without applying treatment.

In conclusion, for patients with moderate hypocalcaemia in the early period following total thyroidectomy, follow-up without treatment seems to be the most effective treatment; avoiding IV treatment might be helpful.

Conflict of interest

The authors declare that they have no conflict of interest.

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