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Hypocalcaemia after Thyroid Surgery for Differentiated Thyroid Carcinoma: Preliminary Study Report

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A B S T R A C T

Hypocalcaemia is one of the most common major complications after thyroid surgery with the wide range of incidence from 6.9 to 46%. Thyroidectomy is usually first choice treatment for differentiated thyroid carcinoma (DTC). The study comprised 46 adult patients operated at Zagreb University Hospital Centre. Intraoperative and postoperative ionized calcium and intact parathyroid hormone (iPTH) were studied. The object of this study is to investigate risk factors, incidence of hypocalcaemia after surgical treatment of differentiated thyroid carcinoma, and the role of iPTH in comparison to ionized calcium as a predictor for hypocalcaemia.

***Key words**: hypocalcaemia, thyroid surgery, differentiated thyroid carcinoma*

Introduction

Postoperative hypoparathyroidism is a well-recognized complication in thyroid surgery. It is estimated that transient hypoparathyroidism after thyroid surgery range from 6.9% to 46%, and for permanent hypoparathyroidism from 0.4% to 33%. The latter may result in calcification of the basal ganglia, cataract formation, and tetany. Clinical symptoms are quite distressing, especially in severe hypoparathyroidism. Several thyroid conditions such as Graves' disease, thyrotoxicosis as a result of hyperactive thyroid adenomas, recurrent goiter, and thyroid carcinoma carry a higher risk to develop transient and permanent hypoparathyroidism postoperatively. Other contributing factors are related to surgical technique, such as devascularization or inadvertent resection of the parathyroid glands[1].

Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (90%) of all thyroid cancers. During the past decades significant increase in the incidence of thyroid cancer was recorded worldwide, mainly due to increase in the incidence of papillary thyroid cancer, probably because of improved diagnostics. In the United States, approximately 37,200 new cases of thyroid cancer are diagnosed yearly. The yearly incidence has increased from 3.6 *per* 100,000 in 1973 to 8.7 *per* 100,000 in 2002, a 2.4-fold increase ($p<0.001$ for trend) and this trend appears to be continuing. Almost the entire change has been attributed to an increase in the incidence of papillary thyroid cancer (PTC), which increased 2.9-fold between 1988 and 2002[2]. In Croatia between 1986 and 2004 incidence has increased 8.6 times in women, and 2.9 times in men[3]. Several controversies currently exist regarding the management of differentiated thyroid cancer. These include the extent of surgical resection, role of radioiodine treatment, thyroxine suppression and treatment of the lymphatic drainage to the neck.

Surgical treatment of thyroid cancer may cause some complications, partially because of the variable anatomy of the neck. These possible complications include the following: hypothyroidism, dysphagia due to damage of the upper laryngeal nerve, vocal cord paralysis after damage of recurrent laryngeal nerve and hypoparathyroidism because of inadvertant parathyroid excision, devascularisation or damage[4]. The object of this study is to investi-

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gate risk factors and incidence of hypocalcaemia after surgical treatment of differentiated thyroid carcinoma.

Materials and Methods

Subjects

This report included all patients who underwent thyroid surgery by two surgeons between February 2010 and April 2011. All surgeries are done using Harmonic scalpel (Ultracision Harmonic Scalpel, Ethicon Endo-Surgery, Inc., Cincinnati, Ohio). Patients gave written informed consent and all procedures were carried out in accord with the Good Scientific Practice Standards of the University Hospital Centre Zagreb, which are based on the ethical standards of the Helsinki Declaration. Patients with previous thyroid surgery or neck dissection, with primary, secondary hyperparathyroidism, and reduced renal function are not included in the study.

Methods

Blood samples for PTH and ionized calcium are taken from peripheral vein in the ward after induction of anesthesia and before skin incision (start), and at the end of surgery (end), intraoperativly, on the evening of surgery (day 0) and on the morning of day 1. Further calcium measurements were performed as clinically indicated. All patients were seen in the outpatients department 2 weeks after surgery (K1).

Serum Parathyroid hormone was measured using IRMA PTH, radioimmunoassay for in vitro determination of parathyroid hormone in human serum and plasma (IMMUNOTECH SAS, Marseille Cedex, France). Reference values in our laboratory are 1-6 pmol/L. The coefficients of variation were found below or equal to 7.5%. Ionized calcium (iCa) was measured on GEM Premier 3000 (Instrumentation Laboratory Company, Lexington, MA, USA). The reference ranges for iCa are 1.12–1.32 mmol/L.

Temporary hypocalcaemia requiring treatment was defined as iCa<1.1 mmol/L or the presence of symptoms i.e. circumoral and distal extremity paraesthesia or carpopedal spasm in the first 2 weeks following thyroidectomy. Treatment consisted of calcium and alfacalcidol replacement until futher follow-up according to the departmental protocol.

All patients filled out a chart in cooperation with the nursing staff during the daily rounds. The patient is asked about typical hypocalcaemia-related symptoms, such as paraesthesia in the face, upper and lower extremities or tetany. Symptoms and their severity are documented, as the supplementation of calcium and/ or vitamin D also. Patients who develop hypocalcaemia will be treated by oral or intravenous calcium supplementation and/or active vitamin D (calcitriol). Patohistological results were collected for all patients in order to rule out inadvertant parathyroid excision (IPE). The definition of permanent hypoparathyroidism in the study was that serum iPTH or iCa levels below the normal range, or calcium and/or vitamin D supplementation necessary to treat hypocalcaemia-related symptoms for more than 12 months in order to rule out late recovery.

Statistical analysis

Statistical analyses were performed using Prism version 5.1 software (GraphPad Software, San Diego, CA, USA) and STATISTICA 8 Software (StatSoft). χ^2-test and student t-tests were used to test differences between groups. Results are presented as mean±standard deviation (SD), unless specified diferently. The threshold for statistical significance was conventionally set at $p<0.05$.

Results

A total of 46 procedures were included in the study, 41 women and 5 men of mean age 44 (range 20 to 50 years) for follicular carcinoma and 43 (range 16 to 73 years) years for papillary carcinoma (Table 1). The indications for surgery and the extent of surgery are shown in Tables 1 and 2. As it can be seen 11 patients had follicular carcinoma and 35 patients papillary carcinoma. Four patients had initialy partial resection of thyroid gland eg. lobectomy, followed by completion thyroidectomy after final pathological results. Autotransplantation of parathyroid tissue was not routinly done in any of cases. Postoperative blood sampling was complete to discharge and after 14 days. Follow-up is still in progress for all patients with hypocalcaemia. In group with follicular carcinoma were 5

TABLE 1
DEMOGRAPHIC DATA

	PC	FC	P*
No.patients	35	11	
Female/male	31/4	10/1	0.714
Mean age (yrs)	43.5±26.16	44.0±8.48	<0.001

FC – follicular carcinoma, PC – papillary carcinoma, p<0.05, * t-test

TABLE 2
POSTOPERATIVE OUTCOMES

	PC (n=35)	FC (n=11)	p
Primary tumor size (cm)	2.01±1.66	1.83±0.95	0.74
Operating time (min)	73.11±33.28	63.18±23.59	0.36
Extent of surgery			
TT	24 (68.5%)	10 (91%)	
Lobectomy	3 (8.5%)	1 (9%)	
ND	8 (23%)	0	

PC – papillary carcinoma, FC – follicular carcinoma, LN – lymph nodes, d – days, TT – total thyroidectomy, LT – lobectomy, ND – neck dissection, n – number

(45%, Table 3) cases of hypocalcemia defined with ionised calcium <1.1 mmol/L or symptoms of hypocalcemia (just 1 patient had symptoms). In 4 cases parathyroid tissue was found in pathohistological specimen, only 1 patient

TABLE 3
POSTOPERATIVE COMPLICATIONS

	PC (n=35)	FC (n= 11)	p
RLN palsy			
Temporary	2	0	0.29
Permanent	0	0	
Hypoparathyroidism			
Temporary	23 (65%)	5 (45%)	
Permanent	4*	1	
Hemorrhage	0	0	
Hematoma	1	0	
Seroma	0	0	
Tracheoesophageal injury	0	0	
Total	26	6	

RLN – recurrent laryngeal nerve, PC – papillary carcinoma, FC – follicular carcinoma, p<0.05, * – follow-up not finished

from this group had temporary hypocalcaemia. Follow up for this group was complete, and only 1 patient developed permanent hypocalcaemia. In a group with papillary carcinoma (35 patients), 23 patients (65%) developed hypocalcaemia after surgery. Only 5 (21%) patient of 23 of them had symptoms of hypocalcaemia. Inadvertent parathyroid excision (IPE) was found in 15 cases, but only 9 of them had temporary hypocalcemia untill this work is published (Table 4). The proportion of patients with IPE and hypocalcaemia 52% (10 of 19) *vs*. 67% (18 of 27) hypocalcaemic patients without IPE was not satistically significant (p<0.632).

TABLE 4
COMPARISON OF PATHOLOGY DATA AMONG DIFFERENT GROUPS

	PC (n=35)	FC (n=11)	p
Primary tumor size (cm)*	2.01±1.66	1.83±0.95	0.734
Multifocality	16 (45.7%)	0	0.005
Extracapsular invasion	8 (22.8%)	0	0.084
Nodal involvement(n)			
Central	4 (11.4%)	0	0.250
Lateral	6 (17.1%)	0	0.142
IPE (n)	15 (42.8%)	4 (36.4%)	0.710

* Mean ± SD, t-test, n – number, IPE – inadvertent parathyroid excision, p<0.05,

Mean ionised calcium (iCa) and mean iPTH values are shown in Figures 1–4. In hypocalcaemiac group with papillary carcinoma mean iCa before start of surgery was 1.07±0.09 and iPTH 6.45±3.74 and at the end of surgery

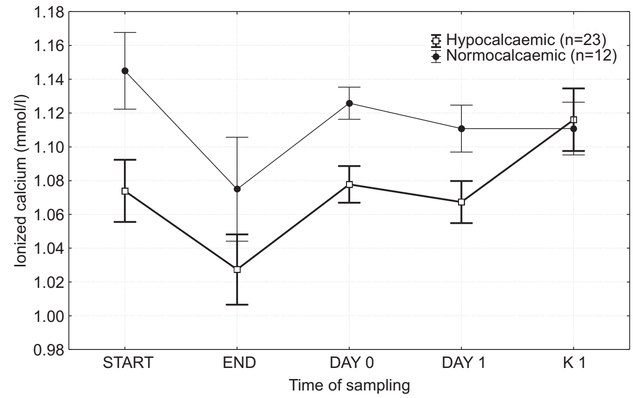

Fig. 1. Changes in ionized calcium levels before (start) and after thyroidectomy for papillary carcinoma in normocalcaemic and hypocalcaemic group. Values represent mean +/– SEM. START – before incision, END – end of surgery, DAY 0 – evening on the day of surgery, DAY 1 – tomorrow morning, K 1 – two weeks after surgery.

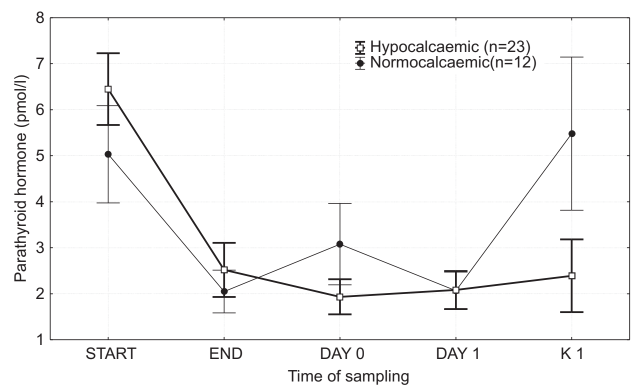

Fig. 2. Changes in parathyroid hormone levels before (start) and after thyroidectomy for papillary carcinoma in normocalcaemic and hypocalcaemic group. Values represent mean +/– SEM. START – before incision, END – end of surgery, DAY 0 – evening on the day of surgery, DAY 1 – tomorrow morning, K 1 – two weeks after surgery.

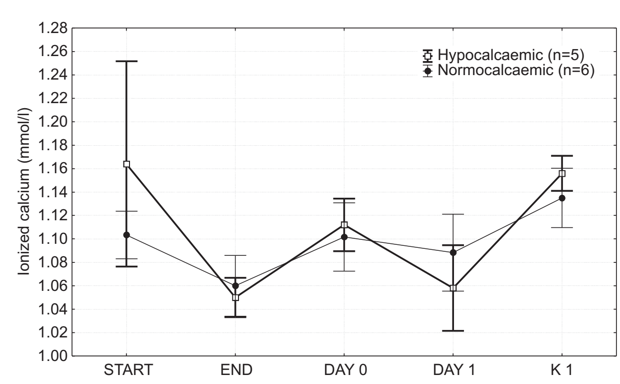

Fig. 3. Changes in ionized calcium levels before (start) and after thyroidectomy for follicular carcinoma in normocalcaemic and hypocalcaemic group. Values represent mean +/– SEM. START – before incision, END – end of surgery, DAY 0 – evening on the day of surgery, DAY 1 – tomorrow morning, K 1 – two weeks after surgery.

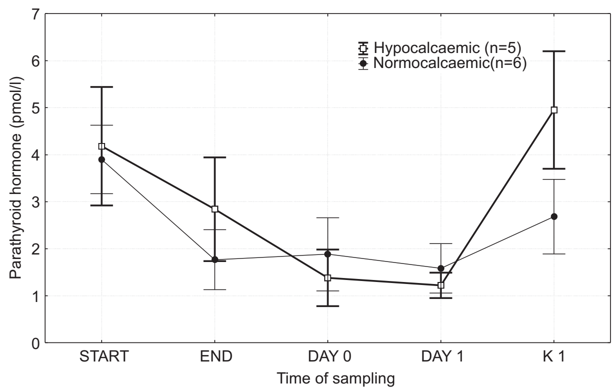

Fig. 4. Changes in parathyroid hormone levels before (start) and after thyroidectomy for follicular carcinoma in normocalcaemic and hypocalcaemic group. Values represent mean +/– SEM. START – before incision, END – end of surgery, DAY 0 – evening on the day of surgery, DAY 1 – tomorrow morning, K 1 – two weeks after surgery.

it droped to 1.03±0.10 mmol/L and iPTH to 2.08±1.98. Trend of both values are same, but difference beetween iCa at start and end, start vs day 0, day 1 and K1 was not statistically significant (t-test), while iPTH was statistically lower in normocalcaemic and hypocalcemic group in the same time points (Figures 1–4). Incidence of hypocalcaemia following TT vs TT+CND or TT vs LT are shown in Table 5. Only in LT vs TT group was significant difference of hypocalcaemia ($p<0.05$, χ^2 test).

TABLE 5
RISK OF POSTOPERATIVE HYPOCALCAEMIA IN RELATION TO NODE DISSECTION

Variable	Patient No	Hypocalcaemic	
		No(%)	p*
TT *vs* TT+CND	30	17 (56.7%)	0.221
	6	5 (83.3%)	
TT *vs* TT+LND	30	17 (56.7%)	0.854
	2	1 (50%)	
TT *vs* LT	30	17 (56.7%)	0.033
	4	0 (0%)	

TT – total thyroidectomy, CND – central neck dissection, LND – lateral neck dissection, LT – lobectomy, $p<0.05$, χ^2-test, No – number of patients

Discussion and Conclusion

Considerable effort has been expended on the prevention of recurrent laryngeal nerve palsy after thyroidectomy, but postoperative hypoparathyroidism and its consequences remain widely underrated. Permanent loss of parathyroid function still occurs after up to 33% of total thyroidectomies[1]. In present study transient hypocalcaemia is higher (60.86%) than in published studies. Possible causes of higher incidence of hypocalcaemia in our study are use of ionized calcium and lower threshold for supplement therapy than in published studies (this was inclusion criteria for transient hypocalcaemia, majority of authors use total calcium which is not an active form of calcium), malignancy as known risk factor for hypocalcaemia, no routine autotransplatation and previous hyperthyreosis as another reason for higher incidence of hypocalcaemia postoperatively (10 cases).

Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4)[2]. Still there are controversies about it. Moo et al., 2011 stated that many surgeons advocate prophylactic central neck lymph node dissections in patients who present with no clinical or radiographic evidence of lymph node involvemen[5]. Neck dissection was therapeutically done in 8 patients (23%) with papillary thyroid carcinoma according to the preoperative clinical and ultrasound examination. Prophylactic neck dissection is not a common practice in our institution unless in high risk patients according to ATA guidelines[2].

Limitations of our study are small sample size, small number of patients with neck dissection, unknown vitamin D status (we presumed normal vitamin D status according to geographical latitude and normal renal function).

In the study of Rajinikanth et al.[6] the incidence of IPE was 12.9% and IPE caused significantly higher rates of temporary and permanent postoperative hypocalcaemia. The search for lower morbidity after total thyroidectomy is a worthwhile exercise for this technically challenging procedure. In our study incidence of IPE is much higher 42.8% in PC group and 36.4% in FC group, and IPE was not found to be a significant factor for the development of hypocalcaemia postoperatively, possibly because preserved function of the remaining parathyroid glands. It is important to emphsize that in only one case 2 parathyroid glands were excized in one patient, and in rest of cases only 1 parathyroid gland was found.

We speculate that the transient hypocalcaemia was caused by mechanical factors (stretching, pinching) or perioperative hemodilution with increased renal excretion of the calcium and increased release of calcitonin, as noted by others.

All surgeries are done using harmonic scalpel (HS). The usefulness of the HS in thyroid surgery has been widely reported, and it provides an alternative to conventional methods of hemostasis[7,8]. The HS uses high-frequency ultrasound energy, which allows the coagulation and cutting of tissues at low temperatures. The HS has been used for cardiac, general, oral, laparoscopic, and gynecologic surgery because of its ability to access narrow operating fields. Several studies have shown that the

HS is a safe method for controlling bleeding and that it shortens the operating time[9]. Similar studies investigating laboratory changes of iCa and iPTH during and after using harmonic scalpel for thyroid operations in DTC are not familiar to authors, and different criteria for hypocalcaemia in published studies makes it difficult to compare results. Foreman et al.[10] published a retrospective cohort study with a statement that the use of harmonic scalpel during thyroidectomy significantlly reduces operative time and postoperative hypocalcaemia. To our opinion there are too many variables between the paired groups that can be source of systemic errors, e.g.: ionized calcium is used for diagnosis of hypocalcaemia without reference values mentioned, values 24 and 48 hours after operation are used, and hypocalcaemia can appear after that period too; second there are patients with hemi and total thyroidectomy in both groups, but number of each operations is not specified in any of groups; third department protocol of substitution therapy isn't mentioned in the study. Further studies are needed to objectives influence of HS on parathyroid tissue in comparison to conventional tehniques[7,8].

The drive towards a shorter hospital stay following total thyroidectomy has led to a number of studies evaluating the use of plasma biochemical markers to predict the development of hypocalcaemia. Thyroid surgery impairs PTH secretion by the parathyroid glands resulting in postoperative parathyroid insufficiency and subsequent development of hypocalcaemia[11].

The measurement of total serum calcium is inaccurate, at least in part, owing to postoperative haemodilution. There is no consensus regarding the definition of temporary hypocalcaemia. The definition of post-thyroidectomy hypocalcaemia differs between various studies and ranges from a corrected serum calcium of 1.8 to 2.1 mmol/L. In addition, reference values differ according to the measurement technique used, which varies between studies[12]. A poor correlation between biochemical and symptomatic hypocalcaemia has been reported.

The value of PTH in predicting post-thyroidectomy hypocalcaemia has been extensively investigated and reported in the literature. Although the use of PTH post-thyroidectomy may allow shorter hospital admission, rapid access to results of postoperative PTH measurement is not widely available in most hospitals. In addition, there is no consensus on the threshold for PTH and the optimal timing for its measurement post-thyroidectomy[11,12].

Conclusion

Type of tumor, multifocality, extent of surgery, and previous hyperthyreosis are risk factors for hypocalcaemia after thyroid surgery for DTC. iPTH is earlier predictor of hypocalcaemia than iCa, which changes slower than iPTH. Futher studies are needed regarding the influence of harmonic scalpel on parathyroid tissue.

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HIPOKALCEMIJA NAKON OPERACIJE ŠTITNJAČE ULTRAZVUČNIM NOŽEM: PRELIMINARNA STUDIJA

S A Ž E T A K

Hipokalcemija je jedna od najčešćih velikih komplikacija nakon operacije štitnjače sa širokim rasponom incidencije od 6,9 do 49%. Tiroidektomija je obično liječenje prvog izbora za diferencirani karcinom štitnjače (DTC). Ova studija uključuje 46 bolesnika operiranih u Kliničkom bolničkom centru Zagreb. Proučavane su intraoperativne i postoperativne vrijednosti ioniziranog kalcija(iCa) i intaktnog parathormona(iPTH). Predmet studije je istraživanje faktora rizika, incidencije hipokalcemije nakon kirurškog tretmana kod DTC-a i usporedba iCa i iPTH kao prediktora hipokalcemije.