

INTRAOPERATIVE PARATHYROID HORMONE MEASUREMENT IN THYROIDECTOMIZED PATIENTS: PRELIMINARY REPORT

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Background. Hypocalcemia is the most frequent complication after thyroid surgery. Intraoperative measurement of parathormone levels (ioPTH) in patients undergoing thyroid surgery has been recently described as an accurate method of predicting postoperative parathyroid dysfunction. The aim of the study was to evaluate utility of ioPTH and parathormone level measured 24 hours after surgery (24PTH) as prognostic factors of hypoparathyroidism and consequent hypocalcemia.

Subjects and Methods. Fifty-four patients (50 females and 4 males) underwent 55 operations: subtotal thyroidectomy (44), total thyroidectomy (8), completion thyroidectomy due to goiter recurrence and cancer (2 and 1 patients, respectively). PTH and serum calcium levels were assessed one day prior to surgery, intraoperatively during wound closure, on the first postoperative day and 2 months after surgery. Hypoparathyroidism was defined as parathormon level less than 15 pg/ml.

Results. Seventeen patients presented ioPTH levels below 15 pg/ml. Twelve of them had low 24PTH levels. Only one patient with ioPTH (but not 24PTH) below 15 pg/ml developed persistent hypoparathyroidism, resulting in low parathormone level 2 months after surgery. Three investigated subjects with ioPTH greater than 15 pg/ml had low 24PTH levels but none of them developed persistent hypoparathyroidism. One patient with ioPTH and 24PTH within reference range presented hypoparathyroidism at the 2-month follow-up, presumably due to postoperative iodotherapy.

Conclusions. This study suggests that ioPTH and 24PTH levels are not useful prognostic factors of persistent hypoparathyroidism but may indicate transient parathyroid gland dysfunction.

Key words: Intraoperative parathyroid hormone assessment – ioPTH – Thyroid surgery

Hypocalcemia is the most frequent complication of thyroid surgery, accounting for longer hospitalization and raise in treatment costs, as well as deteriorating patients' quality of life. Asymptomatic hypocalcemia may occur in as many as 50 % - 87 % patients (MCHENRY et al. 1994; LOMBARDI et al. 2004; SZUBIN et al. 1996). Clinical manifestations develop in 10 % of surgically treated patients and are definite in 17 % of the symptomatic cases (ROSATO et al. 2004).

Multiple factors impair the function of parathyroid glands, such as injury, devascularization and inadvertent excision being the most obvious mechanisms leading to hypoparathyroidism after thyroid surgery. They

also explain the fact of higher incidence of parathyroid dysfunction in patients with thyroid carcinomas, as well as with substernal and recurring goiters (MCHENRY et al. 1994; RICHARDS et al. 2003; ROSATO et al. 2004; LOMBARDI et al. 2004).

This study was designed to prospectively assess the utility of intraoperative PTH measurement in predicting impairment of parathyroid function. Defining a subgroup of patients with high risk of postoperative hypoparathyroidism can result in early calcium and vitamin D supplementation, more careful postoperative monitoring and revised time of hospital stay while patients with intact parathyroids condition for early discharge.

Subjects and methods

Subjects. Fifty-four (50 females and 4 males) of all the patients treated in the site of research from mid-August through mid-October 2005 participated in this study. Patients who failed to undergo all tests were excluded. One patient was excluded due to definite hypoparathyroidism prior to hospitalization.

Informed consent was obtained from all subjects of the study. The protocol was approved by Ethics Committee of the Medical University of Lodz.

Surgical procedures. The patients were surgically treated for thyroid diseases. They underwent subtotal thyroidectomy (44 patients), total thyroidectomy (8 patients) or completion thyroidectomy due to goiter relapse and cancer recurrence (2 and 1 patients, respectively). One patient underwent subtotal thyroidectomy followed by completion thyroidectomy after histopathological finding of papillary carcinoma.

Blood samples. Four blood samples were collected from each patient to determine PTH level. Serum calcium level was assessed simultaneously. The basal PTH and calcium values (0PTH, 0Ca) were measured in the sample obtained on the day of admission, being a day prior to surgery. Intraoperative PTH and calcium levels (ioPTH, ioCa) were assessed in the blood specimen drawn from peripheral intravenous line during wound closure. Subsequent assessment of PTH (24PTH) and Ca (24Ca) was performed on the postoperative day, 24 hours after the surgery, and was considered decisive of diagnosing normo- or hypoparathyroidism. None of the subjects received calcium treatment until that moment. The ultimate sample was collected during a follow-up visit 2 months after operation. Patients previously administered oral calcium supplementation were asked to stop the treatment for two days prior to the visit unless symptoms occur. All patients were able to obey this request. Low follow-up PTH level was qualified as permanent hypoparathyroidism.

Laboratory assays and reference values. To assess PTH we used electrochemiluminescence immunoassay (ECLIA) on Roche Elecsys analyzer available at the site of the study. The assay was completed by a technician in approximately 30 minutes. For the purpose of this study we adopted the PTH reference levels of the site's laboratory defined as values ranging from 15 – 65 pg/mL. Other measurements were performed by means of standard assays. Reference serum calcium level in our laboratory ranges from 4.2 to 5.1 mEq/l.

Results

All patients enrolled in the study had basal PTH in normal range. The mean values of 0PTH and 0Ca were 45.55 ± 14.87 pg/ml and 4.88 ± 0.26 mEq/l, respectively. None of the patients was hypocalcemic. Six subjects presented elevated 0Ca which did not exceed 5.9 mEq/l and was accompanied by normal PTH value in each of these cases.

Mean PTH dropped to 34.71 ± 23.74 pg/ml immediately after the operation. Seventeen subjects (30.9 %) presented ioPTH below 15 pg/ml. In this group of patients, three (17.7 %) subjects presented low ioCa and one (diagnosed of hyperparathyroidism) had raised ioCa. In 12 of 17 patients with low ioPTH, hypoparathyroidism was still observed on postoperative day one. Calcium concentration was decreased in 9 of these subjects.

Two patients (3.6 %) showed hypoparathyroidism at the follow-up visit. One of them had ioPTH level below 15 pg/ml ($=10.11$ pg/ml) but 24PTH within normal range ($=25.96$ pg/ml). The other patient had both ioPTH and 24PTH within the normal values (39.28 and 41.15 pg/ml, respectively). This subject underwent iodotherapy for PTC, which may explain the parathyroid gland impairment. None of these patients showed hypocalcemia.

Only one patient (1.8 %) presented hypocalcemia at the follow-up visit. This fact did not allow for statistical analyses. However, it should be noticed that the subject was also hypocalcemic intraoperatively as well as on the postoperative day one, and presented dramatically decreased values of ioPTH and 24PTH (3.97 pg/ml and 4.03 pg/ml, respectively). In this patient PTH level at the follow-up raised to low-normal values (1mPTH= 16.56 pg/ml) and only mild hypocalcemia was present (1mCa level of 4.1 mEq/l).

An interesting observation was made regarding mean PTH changes within the first 24 hours after surgical procedure. In 12 of 17 (70.6 %) patients with low ioPTH an increase in parathormone level was observed. A mean raise was 35.4 %. On the contrary, 30 (78.9 %) of the remaining 38 patients with normal ioPTH presented decrease in parathormone on postoperative day one, including 2 patients (5.7 %) with 24PTH below 15 pg/ml despite normal ioPTH. In this group of subjects an average decrease of 24,4 % was observed.

Accuracy of the employed methods. In the group of 17 patients with low ioPTH, 10 (58.8 %) developed laboratory signs of hypocalcemia on postoperative day

Table 1
Distribution of thyroid diseases in the studied subjects

Preoperative diagnosis by fine needle aspiration	Number of patients
Non-toxic nodular goiter (NTG) – total	28 (51.85 %)
Retrosternal NTG	1
NTG relapse	1
Toxic nodular goiter (TG) – total	23 (42.59 %)
TG relapse	1
Thyroid neoplasm	3 (5.56 %)
Papillary cancer (PTC)	2
PTC reoccurrence	1
Follicular neoplasm	1
PTC in postoperative material (patient qualified for reoperation)	1

Table 2.
Parathyroid hormone and serum calcium concentrations in the studied subjects at different time-points

Value	OPTH	ioPTH	24PTH	1mPTH	0Ca	ioCa	24Ca	1mCa
mean	45.55	34.71	26.36	40.16	4.88	4.46	4.41	4.60
SD	14.87	23.74	15.50	18.98	0.26	0.38	0.43	0.26
max	85.10	95.57	68.77	96.55	5.90	6.20	5.30	5.50
min	17.01	3.97	4.03	8.60	4.40	3.90	3.50	4.10

Table 3
Allocation of patients in respect of PTH value (cut-off at 15 pg/ml) at different time-points. Groups with PTH below 15 pg/ml are shaded; numbers in parentheses indicate hypocalcemic patients in each group

Preoperative	Intraoperative	Postoperative	Follow-up
55 pts PTH>15 (0 hypocalcemic)	17 pts PTH<15 (4 hypocalcemic)	12 pts PTH<15 (8 hypocalcemic)	12 pts PTH>15 (1 hypocalcemic)
		5 pts PTH>15 (2 hypocalcemic)	1 pt PTH<15 (0 hypocalcemic)
	38 pts PTH>15 (6 hypocalcemic)	3 pts PTH<15 (1 hypocalcemic)	4 normoPTH (0 hypocalcemic)
		35 pts PTH>15 (6 hypocalcemic)	3 pts PTH>15 (0 hypocalcemic)
			1 pt PTH<15 (0 hypocalcemic)
			34 normoPTH (0 hypocalcemic)

Table 4
Sensitivity and specificity of the predictive value of ioPTH assessment

ioPTH cut-off [pg/ml]	N	Sensitivity	Specificity
17.5	19	64.71%	78.95%
15.0	17	58.82%	81.58%
12.5	15	47.06%	81.58%
10.0	10	35.29%	89.47%
7.5	4	23.53%	100.00%

N – number of subjects with ioPTH below the cut-off value

Table 5

Sensitivity, specificity and predictive values of different parameters in the prediction of post-thyroidectomy hypocalcemia.

Parameter	Sensitivity	Specificity	PPV	NPV
ioPTH < 15 pg/ml	58.82%	81.58%	58.82%	81.58%
DioPTH70	52.94%	89.47%	69.23%	80.95%
ioPTH < 15 pg/ml and Δ ioPTH70	47.06%	89.47%	66.67%	79.07%
oPTH < 15 pg/ml and/or Δ ioPTH70	64.71%	81.58%	64.71%	81.58%

one. The sensitivity and specificity of this test were 58.8 % and 81.6 %, respectively. The positive predictive value (PPV) of ioPTH cut-off at 15 pg/mL was 58.8 % and the negative predictive value (NPV)—81.6 %.

Some authors reported ioPTH vs. baseline PTH level changes as a patent predictive factor of post-thyroidectomy hypocalcemia (SCURRY 2005, LO 2002). In our study, a drop of PTH at the end of surgery of more than 70 % (Δ ioPTH70) was observed in 8 of 10 (80.0 %) patients with low ioPTH and postoperative hypocalcemia. Moreover, 10 of 12 (83.3 %) patients with low ioPTH who continued to present low PTH values on postoperative day one, had a Δ ioPTH exceeding 70 %. However, most of the patients with low ioPTH who showed no symptoms of hypocalcemia (4 of 7 patients, 57.1 %) also presented Δ ioPTH70. On the contrary, in the group of 7 hypocalcemic patients with ioPTH over 15 pg/ml only one subject (14.3 %) experienced PTH drop of more than 70 % at the end of surgery.

DioPTH70 proved a 52.9 % sensitivity and a 89.5H % specificity as a predictor of hypocalcemia in our subjects. The PPV and NPV were 69.2 % and 80.9 %, respectively.

Since these results were not satisfactory, we investigated whether the combination of ioPTH below 15 pg/ml and Δ ioPTH70 would be more accurate prognostic factor of hypocalcemia in thyroidectomized patients. Our data showed unexpectedly a lower sensitivity, PPV and NPV, and an equal specificity of this analysis, comparing to Δ ioPTH70 alone. Eventually, we found that the sensitivity is relatively highest (64,71%) if either ioPTH below 15 pg/ml or Δ ioPTH70 was considered, although other predictive values failed to prove more accurate in this test. Table 5 shows the results.

Discussion

Serum calcium assessment in symptomatic patients has been the conventional method of the postoperative parathyroid monitoring, requiring extended hospital-

ization time (Scurry et al. 2005, QUIROS et al. 2005). Prognostic value of early postoperative calcium level changes was also reported by some authors (MAROHN and LACIVITA 1995; ADAMS et al. 1998). The utility of these studies in terms of early patient discharge and cost effectiveness was limited and no definite cut-off value was found (LAM and KERR 2003; WARREN et al. 2004). BELLANTONE et al. (2002) and BOVE et al. (2004), among others, suggested the administration of substitutive calcium and vitamin D treatment in all or high-risk patients who undergo thyroid surgery. This idea has not been commonly accepted due to the hindrance in detection of hypocalcemia and questionable cost-effectiveness (Lo et al. 2002; Lo 2003).

Recently the PTH assessment which has been used in parathyroid surgery for more than two decades, was introduced as an early predictor of parathyroid dysfunction in thyroidectomized patients (IRVIN et al. 1993; WARREN et al. 2002; LO et al. 2002). It is an element of an innovative approach to thyroid surgery, along with neuromonitoring, usage of harmonic scalpel and videoscopic techniques (DRALLE 2006). Although a growing number of papers have addressed the issue, contradictory data has been reported regarding cost-effectiveness, sensitivity, specificity, and optimal timing of PTH assessment, from enthusiastic opinions from LOMBARDI et al. (2004), VESCAN et al. (2005) and others to a more sceptic attitude presented by WARREN et al. (2004) and HIGGINS et al. (2004), to abandoning further research by others (DEL RIO et al. 2005).

TH assessment at different time-points was investigated. Recovery room PTH measurement proves useful in terms of outpatient surgery. VESCAN et al. (2005) showed 95 sensitivity of 1-hour postoperative PTH assessment with cut-off level of 1.6 pmol/l (equivalent of cca15.5 pg/ml and 99 specificity of this method with a cut-off value of 1.1 pmol/l (cc. 10.5 pg/ml. LAM and KERR (2003) showed earlier a 100 specificity and sensitivity for the cut-off value of 8 pg/ml at the same time-point; however, their PTH reference values were 7 to

50 pg/ml Both LAM and KERR (2003) and VESCAN et al. (2005) emphasized that PTH levels may vary by institution and by the type of biochemical assay. CHIA et al. (2006) investigated PTH level 8 hours after the operation and found a 100 % sensitivity and 90.5 % specificity for cut-off value of 15 pg/ml. Recent studies have shown that the nadir of PTH level occurs 4 hours postoperatively. LOMBARDI et al. (2004) described 100 % specificity and sensitivity for PTH minor of 10 pg/ml at 4 and 6 hours postoperatively.

Although a delay in obtaining PTH level or sequential assessment may improve accuracy of the tests, the ability to autotransplant inadvertently removed or devascularized parathyroid tissue is a crucial advantage of intraoperative approach (LO et al. 2002; RICHARDS 2006). Optimistic data from LINDBLOM et al. (2002) showed 90 % sensitivity and 75 % specificity of low ioPTH in predicting biochemical hypocalcemia and 71 % sensitivity and 81 % specificity in predicting symptomatic hypocalcemia. RICHARDS et al. (2006) has recently reported that in her study ioPTH of less than 10 pg/ml had a sensitivity of 80 % and a specificity of 100 % (PPV 100 % and NPV 91 %) for the development of symptomatic hypocalcemia. Both of these studies prove superior value of PTH assay in comparison to day 1 serum calcium concentrations.

Our study primarily focused on evaluation of the utility of ioPTH assessment in determining postoperative dysfunction of parathyroid glands after thyroid surgery. The results showed poor sensitivity of all the employed methods. Little more than a half of the patients with laboratory findings of hypocalcemia were diagnosed by means of ioPTH at cut-off level of 15 pg/ml and DioPTH70 measurement. Maximal sensitivity of 64.7 % is intolerable for clinical application. This data is contradictory to the outcomes reported by other authors. LO et al. (2002) reported a 100 % sensitivity and a 72 % specificity of a more than 75 % decline in quick PTH at 10 minutes after thyroidectomy. Limited

number of cases (N=4) discouraged us from analyzing the ioPTH cut-off value at 7.5 pg/ml. However, the finding that all of them developed hypocalcemia appears to be consistent with communications from other researchers (LAM and KERR 2003; SCURRY et al. 2005).

Nevertheless, we conclude that the lack of sensitivity and little PPV is not discouraging. We shifted our aim to finding a test indicating uncomplicated cases. Fairly high specificity and NPV proves the usefulness of the described methods in identifying patients with low risk of post-thyroidectomy hypocalcemia, although our findings require validation by further research before clinical application.

However, our study showed evident limitations. One of them could be the protocol being based on laboratory tests without any reference to clinical signs and symptoms. Most of the patients remained asymptomatic despite calcium level drop. Postoperative calcium decline, but not PTH decline was described in patients who underwent surgical treatment without cervical exploration (LO et al. 2002). Moreover, DEL RIO (2005) reported that serum PTH at 24 hours postoperatively identified only 49 of 101 patients with clinical hypocalcemia, suggesting that the remaining cases could not be correlated to hypoparathyroid condition. Therefore, it seems impossible to achieve 100 % accuracy of the tests based on laboratory findings only. Symptomatic hypocalcemia will be considered in further studies. On the other hand, the subjective human factor was excluded in this study.

Even though the methodology requires further research, we believe that the parathyroid hormone assessment is becoming a novel, potentially valuable tool in thyroid surgery.

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