

CLINICAL STUDY

Hypocalcemia – the most common complication after total thyroidectomy

Cmilansky P, Mrozova L

Poliklinika Sekcov, Wesper, sro, Presov, Slovakia. emilo@post.cz

Abstract: *Objectiva:* Postoperative intact parathyroid hormone (iPTH) levels and some other factors as a predictor of hypocalcemia are analyzed in 115 patients after TTE.

Background: Postoperative hypocalcemia is the most common complication observed after total thyroidectomy (TTE). It is not easy to predict in which patients this complication will occur. We adopted and implemented a novel method to predict this complication – monitoring of postoperative intact parathyroid hormone (iPTH) levels.

Methods and results: Prospective study involves 115 patients. From January till December 2010 we performed 111 TTE and 4 completion thyroidectomies (hemithyroidectomy (HTE) after previous HTE). Gender and age of patients, final histopatology diagnosis, number of parathyroid glands visible during operation, duration of operation and surgeon were factors that did not influence development of postoperative hypocalcemia. A hospital stay was prolonged in patients with hypocalcemia. iPTH level morning after surgery less than 15 pg/ml was a statistically significant predictor of postoperative hypocalcemia. Sensitivity, specificity, positive and negative predictive value of iPTH<15 pg/ml for predicting postoperative hypocalcemia were 71 %, 99 %, 97 % and 86 %, respectively. Sensitivity of iPTH<15 pg/ml in predicting symptomatic postoperative hypocalcemia was 100 %.

Conclusion: Measuring iPTH levels morning after TTE allows prediction of subsequent hypocalcemia with a high sensitivity, specificity, PPV and NPV. Normal iPTH levels ruled out development of hypocalcemia symptoms. Patients with normal iPTH can be safely discharged and the overtreatment of postthyroidectomy patients with calcium and/or vitamin D supplements can be also avoided (Tab. 2, Fig. 3, Ref. 29). Text in PDF www.elis.sk.
Key words: thyroid surgery, hypocalcemia, hypoparathyroidism, parathormone.

Hypocalcemia is well known and the most frequent complication of thyroid surgery. In past only serum calcium levels were used to monitor this complication. But a calcium decrease can take sometimes 48 or more hours. Some authors propose risk factors (gender, thyrotoxicosis, cancer, retrosternal goitre) of postoperative hypocalcemia (1, 2, 3). It is impossible to predict the risk for each individual patient and make decisions regarding duration of hospital stay or treatment strategy upon this risk factors. We adopted and routinely use a novel method – postoperative intact parathormone levels monitoring. We believe that this is the first prospective study on this topic in our country.

Incidence of hypocalcemia is reported from 1.7 to 68 % (1, 2, 3, 4). It is usually mild, but sometimes is severe. As for duration it can be transitory, shorter than 6 months (most often), or permanent – longer than 6 months (1, 2). Patients must undergo

close postoperative observation and laboratory evaluations. The reasons for postoperative hypoparathyroidism that leads to hypocalcemia are injury or devascularisation of a parathyroid gland, accidental removal of 1 or more parathyroid glands, hematoma formations (3, 4, 5, 6). Hospital stay must be often extended due to this complication (7, 8). Some authors advocate a policy of early discharge by treating all patients with calcium and/or vitamin D supplements regardless of parathyroid gland function (7). This practice leads in many patients to overtreatment and could delay the diagnosis and appropriate treatment of hypoparathyroidism (9, 10). It is not easy to predict in which patient hypocalcemia will occur. Clinical and biochemically relevant predictive factors of postoperative hypocalcemia constitute a controversial topic in the literature (11–14). The aim is to identify patients with low risk of developing hypocalcemia who could be discharged early and those who need treatment and close monitoring. Recent studies have described the role of parathyroid hormone alone or combined with serum calcium levels as a predictive factor of hypocalcemia after thyroidectomy (11–14). This study was designed to prospectively assess the utility of postsurgical iPTH levels in predicting postoperative hypocalcemia in total thyroidectomy.

We also evaluate correlations between other factors (patient age and gender, histopatology final diagnosis, number of parathyroid glands identified during surgery, duration of surgery, surgeon's experience, duration of hospital stay) and hypocalcemia after total thyroidectomy.

Poliklinika Sekcov, Wesper, sro, Presov, Slovakia

Address for correspondence: P. Cmilansky, MD, Poliklinika Sekcov, Wesper, sro, Jurkovicova 19, SK-080 01 Presov, Slovakia.
Phone: +421.903774660

Acknowledgement: I would like to thank prof. MUDr. Astl J., CSc., Department of ENT, head and neck surgery, Na Homolce Hospital, Prague, Czech Republic who helped me to start with thyroid surgery. My thanks also belongs to prof. MUDr. Starek I., CSc., ENT clinic, Faculty Hospital Olomouc, Czech Republic and Doc. MUDr. Fryšák Z., CSc., 3rd intern clinic, Faculty Hospital Olomouc, Czech Republic for critical revision and for support to organise this study.

Methods

Demographics. A prospective clinical study was performed from January 2010 till December 2010. 115 consecutive patients (111 primary total thyroidectomy, 4 completion thyroidectomy after previous hemithyroidectomy) were followed up and underwent analysis regarding postoperative parathyroid function. Of these, 16 (14 %) were male and 99 (86 %) were female. Mean patient age was 54 (SD 13, median 54, range 29–78) years. Patients operated because of concomitant parathyroid gland disease were not included in the study.

Surgery. Standard cold steel open total thyroidectomy or completion thyroidectomy were performed. Hemostasis was obtained by bipolar coagulation and polyglactin 910 (Vicryl) vessel ligations. Recurrent laryngeal nerves were visualised in every case by use of magnifying lenses. Every effort was made to identify and preserve all parathyroid glands. In 3 cases of unintended parathyroid gland excision the gland was autotransplanted into sternocleidomastoid muscle at the end of operation. (15).

Laboratory evaluations. According to our protocol serum calcium levels (sCa) were measured once daily at 6 am on postoperative days 1, 2 and 4. Serum iPTH levels were determined at 6am on postoperative day 1. A commercially available intact PTH assay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany) was used. Normal laboratory ranges of iPTH set by our laboratory using this test is 15–65 pg/ml (16)

6 months after surgery sCa and iPTH were measured again. 3 days before these measurement any treatment with calcium and/or vitamin D supplements was stopped. We define postoperative hypocalcemia as sCa < 2 mmol/l. Although the normal range is 2.1–2.6 mmol/l, clinically significant hypocalcemia is uncommon if sCa is greater than 2 mmol/l and this arbitrary figure is commonly quoted in the published work (9). We define hypoparathyroidism as iPTH < 15 pg/ml (iPTH below normal range). We used this value as a cut-off point for calculating sensitivity a predictive values of iPTH in predicting postoperative hypocalcemia. This value is often used in many studies (17, 18, 19). Some authors in their studies looked for other values of iPTH as a cut-off point to obtain better sensitivity, or specificity or PPV/NPV: 13 pg/ml (20), 12 pg/ml (21, 22). If sCa and iPTH levels return to normal within 6 months, hypocalcemia and hypoparathyroidism are classified as transient, otherwise as permanent. We followed signs of hypocalcemia (paresthesia, cramps, tetany).

Treatment. Only symptomatic patients with sCa > 2 mmol/l were supplemented with oral calcium 0.5–2 g per day. Those with sCa 1.8–2 mmol/l obtained 0.5–2 g of oral Calcium supplement, while in cases of sCa < 1.8 mmol/l and with severe symptoms calcium was administered intravenously and orally. Vitamin D analogue (calcitriol) was administered in cases with low sCa and iPTH only after endocrinology consultation and on recommendation.

Hospital stay

Hospitalization was at least 4 days. It was prolonged depending on the patient status and complication occurrence.

In each patient following factors were observed: gender, age,

final histopathologic diagnosis, number of parathyroid glands identified and preserved during surgery, duration of surgery, surgeon's experience, duration of hospital stay.

Diagnoses were divided into groups according classification ICD-10. 17 (15 %) patients were operated on for a malignant thyroid tumor (in 16 patients it was papillary carcinoma, in 1 patient final histology revealed diagnosis of malignant B lymphoma). 27 (23 %) patients had thyreotoxicosis. Number of parathyroid gland visible and preserved during surgery were 0–4. 4 glands were visible in 18 cases (16 %), 3 in 47 (41 %), 2 in 33 (29 %), 1 in 16 (14 %) and none in one case.

Surgeon's experience and duration of surgery

Two surgeons participated in the study (one operated 38 (33 %), another 77 patients (67 %)). Duration of surgery was measured in minutes from skin incision to final closure of a operation wound. Average duration of surgery was 108 minutes (SD 29, median 100, range 45–230).

Statistical analysis

Continuous variables were summarized with descriptive statistics (n, Mean, STD, Minimum, Median, and Maximum). Discrete variables were displayed in frequency tables (n, %). All testing were two-sided tests with the criteria set at $\alpha=0.05$. A p-value of <0.05 was considered statistically significant. The result of the formal hypothesis have been analyzed using standard methods of hypothesis testing – tests on contingency tables, t-test and ANOVA. The sensitivity was calculated, as well as the specificity, negative predictive value (NPV), positive predictive value (PPV), and the general accuracy of the postoperative hypocalcemia determination.

Results

Of the 115 patients included in the study, 73 patients (64 %) were normocalcemic after surgery. 42 patients (36 %) developed hypocalcemia, 22 (19 % of the total) of them developed symptomatic hypocalcemia, 20 (17 %) were asymptomatic (Fig. 1). 84 patients (73 %) showed normal iPTH levels after surgery, 31 patients (27 %) had low iPTH (Fig. 2). After 6 months only 3 patients were hypocalcemic but iPTH levels were normal in all patients.

In patients without postoperative hypoparathyroidism mean (SD) postoperative sCa level on day 1 was 2.18 (0.14) mmol/l, in patients with postoperative hypoparathyroidism 1.96 (0.12) mmol/l. This difference was statistically significant ($p<0.001$). Differences in postoperative sCa level on day 2 and day 4 in patients without hypoparathyroidism and in patients with hypoparathyroidism are statistically significant (2.18 (0.13) resp. 1.91 (0.13) on day 2, 2.25 (0.12) resp. 1.92 (0.17) on day 4). Difference in sCa level after 6 months between these groups is statistically significant too (2.32 (0.11) resp. 2.16 (0.15)) (Fig. 3).

iPTH level. Of the 84 patients with normal iPTH values, 72 were normocalcemic, 12 had laboratory hypocalcemia without symptoms and none had symptomatic hypocalcemia. Of the 31 patients with low iPTH, 22 had hypocalcemia with symptoms, 8 had asymptomatic hypocalcemia and one patient remained nor-

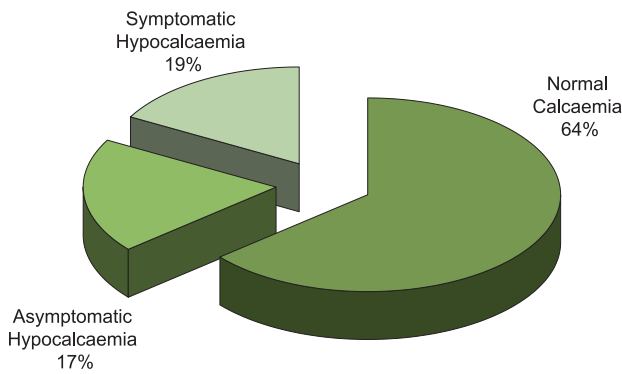


Fig. 1. Proportion of Hypocalcaemia.

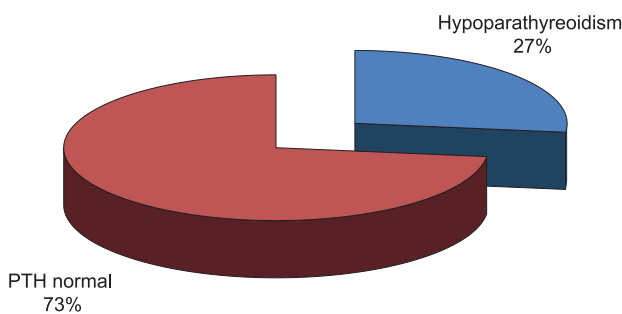


Fig. 2. Proportion of Hypoparathyroidism.

mocalcemic. Sensitivity, specificity, PPV and NPV of iPTH<15 pg/ml for predicting the development of hypocalcemia were 71 %, 99 %, 97 %, 86 % (Tab. 1) and for predicting symptomatic hypocalcemia 100 %, 90 %, 71 %, 100 % respectively (Tab. 2).

We found no statistical difference of postoperative hypocalcemia on gender, age, final histopathology diagnosis, number of identified parathyroid glands, duration of surgery and surgeon's experience.

Hospital stay. The mean hospital stay (SD) was 8 (3) days (range 4–18 days). Hypocalcemia and hypoparathyroidism prolonged hospital stay. This difference was statistically significant ($p < 0.001$)

Discussion

Hypocalcemia is a common complication after total thyroidectomy. The main problem related to hypocalcemia after thyroidectomy is the long hospital stay. Patients must undergo close postoperative observation and frequent laboratory evaluations. This leads to increased costs.

The incidence of hypocalcemia varies from 1.7 to 68 % (1–4). This variability might reflect different definition criteria and differences in perioperative treatment with calcium. The incidence of hypocalcemia in our study was 36 %, in 19 % it was a symptomatic hypocalcemia. The incidence of hypocalcemia in our study is relatively high. But we treat only symptomatic patients or patients with $sCa < 2$ mmol/l with calcium and/or vitamin D supplements. We do not treat all patients regardless of residual parathyroid gland function. The policy of treating all patients is advocated by some authors (7). We do not use this strategy of treating all patients be-

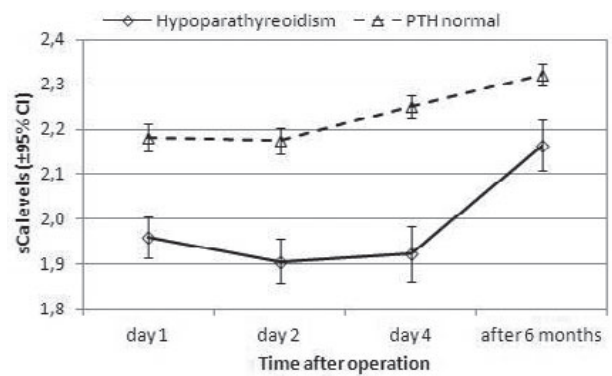


Fig. 3. sCa levels of patients with hypoparathyroidism and patients with iPTH normal. $P < 0.001$ for all times after operation.

cause of risk of administering calcium therapy to normocalcemic patients and inhibiting the resumption of parathyroid glands. Moreover the true incidence of hypocalcemia is concealed and diagnosis of hypoparathyroidism is delayed if this treatment policy is used.

Close monitoring of serum calcium levels was proposed to detect postoperative hypocalcemia. However, the lowest concentrations of serum calcium is not usually reached until 48 hours after surgery (23).

Hypocalcemia after thyroidectomy depends on many factors, but deterioration of the parathyroid function is the decisive factor. The half life of the parathyroid hormone is only 2–5 minutes. The deterioration in the function of the parathyroid glands during surgery has a rapid effect on the serum parathyroid hormone concentration. (24, 25) Early serum PTH assay is a promising method to distinguish early normocalcemic patients from hypocalcemic ones, considering that lower PTH levels have been shown to be significantly correlated with patients developing postoperative hypocalcemia (3, 4).

In our study iPTH determined morning after surgery was found to be within normal levels in 84 patients (73 %), 31 patients (27 %) had low iPTH. The sensitivity of iPTH<15 pg/ml in predicting the development of hypocalcemia was 71 % and specificity, 99 %. The positive predicting value was 97 % and negative predicting value was 86 %. The determining of parathormone levels was even more useful in predicting the development of hypocalcemic symptoms.

Tab. 1. Calcaemia during the postoperative period based on the concentration of iPTH determined 1 day after the operation.

iPTH	Hypocalcaemia	Normal Calcaemia	Total
Low (iPTH<15)	30	1	31
Normal (iPTH≥15)	12	72	84
Total	42	73	115

$p < 0.001$. Diagnostic performance: sensitivity 71 %; specificity 99 %; positive predictive value 97 %; negative predictive value 86 %; general accuracy 89 %

Tab. 2. Symptoms of hypocalcaemia during the postoperative period based on the concentration of iPTH determined 1 day after the operation.

iPTH	With symptoms	Without symptoms	Total
Low (iPTH<15)	22	9	31
Normal (iPTH≥15)	0	84	84
Total	22	93	115

$p < 0.001$. Diagnostic performance: sensitivity 100 %; specificity 90 %; positive predictive value 71 %; negative predictive value 100 %; general accuracy 92 %

In this case, the sensitivity of iPTH<15 pg/ml was 100 % and specificity, 90 %. All 84 patients with iPTH>15 pg/ml remained symptoms free. The normal iPTH postoperative levels ruled out subsequent development of hypocalcemic symptoms. These patients could be safely discharged the day after surgery. iPTH<15 pg/ml is not always associated with symptoms of hypocalcemia. Of the 31 patients with low iPTH, 9 remained symptoms free, 22 were symptomatic. These patients would require monitoring of the calcemia and/or calcium or vitamin D supplement treatment.

6 months after surgery all but 3 patients were normocalcemic. iPTH levels returned to normal ranges in all patients of the study and thus permanent damage to all parathyroid glands and permanent hypoparathyroidism were excluded in all our patients.

Our results coincide with most of the informations published. Several studies show that low serum iPTH levels during postoperative period is a predictive factor for hypocalcemia (11, 12, 14, 20, 26–29).

The main clinical usefulness of the normal iPTH test is to identify patients with low risk of developing hypocalcemia who could be discharged earlier in safety without treatment. By contrast, a low iPTH require monitoring of calcemia and treatment if needed (9).

Measuring iPTH levels morning after TTE allows prediction of subsequent hypocalcemia with a high sensitivity, specificity, PPV and NPV. Normal iPTH levels ruled out development of hypocalcemia symptoms. Patients with an undetectable PTH should be commenced early on combination therapy with calcium and calcitriol to prevent development of severe hypocalcemia. Patients with normal iPTH levels can be discharged early and safe. The overtreatment with calcium or vitamin D supplements can be avoided. Normal iPTH level also proves that at least one functioning parathyroid gland was spared.

References

- Falk S.** Complications of Thyroid Surgery: Hypocalcemia, Hypoparathyroidism. New York, NY: Raven Press; 1990.
- Reeve T, Thompson NW.** Complications of thyroid surgery: how to avoid them, how to manage them, and observations on their possible effect on the whole patient. *World J Surg* 2000; 24 (8): 971–975.
- Quiros RM, Pesce CE, Wilhelm Sm et al.** Intraoperative parathyroid hormone levels in thyroid surgery are predictive of postoperative hypothyroidism and need for vitamin D supplementation. *Am J Surg* 2005; 189 (3): 306–309.
- Demeester-Mirkine N, Hooghe L, Van Geertudyen J et al.** Hypocalcemia after thyroidectomy. *Arch Surg* 1992; 127: 854.
- Pattou F, Combemale F, Fabre S et al.** Hypocalcemia following thyroid surgery: incidence and prediction of outcome. *World J Surg* 1998; 22 (7): 718–724.
- Shaha AR, Burnett C, Jaffe BM.** Parathyroid autotransplantation during thyroid surgery. *J Surg Oncol* 1991; 46 (1): 21–24.
- Shahai A, Symes A, Jedd T.** Short stay thyroid surgery. *Br J Surg* 2005; 92: 58–59.
- Marhon MR, Lacivita KA.** Evaluation of total/near total thyroidectomy in short stay hospitalization: safe and cost effective. *Surgery* 1998; 118(6): 943–944.
- AES Guidelines 06/01 Group.** Australian Endocrine Surgeons Guidelines AES06/01. Postoperative Parathyroid Hormone measurement and early discharge after total thyroidectomy: analysis of Australian data and management recommendations. *ANZ J Surg* 2007; 77: 199–202.
- Huang SM.** Do we overtreat post-thyroidectomy hypocalcemia? *World J Surg* 2012 Apr 11 (Epub ahead of print)
- Lindblom P, Westerdahl J, Bergenfels A.** Low parathyroid hormone levels after thyroid surgery: a feasible predictor of hypocalcemia. *Surgery* 2002; 131 (5): 515–520.
- Lombardi CP, Raffaelli M, Princi P et al.** Early prediction of postthyroidectomy hypocalcemia by one single iPTH measurement. *Surgery* 2004; 136 (6): 1236–1241.
- Higgins KM, Mandell DL, Govindaraj S et al.** The role of intraoperative rapid parathyroid hormone monitoring for predicting thyroidectomy-related hypocalcemia. *Arch Otolaryngol Head Neck Surg* 2004; 130 (1): 63–67.
- Richards ML, Bingener-Casey J, Pierce D, Strodel WE, Sirinek KR.** Intraoperative parathyroid hormone assay: an accurate predictor of symptomatic hypocalcemia following thyroidectomy. *Arch Surg* 2003; 138 (6): 632–636.
- Niederle B, Roka R, Brennan MF.** The transplantation of parathyroid tissue in man: development, indications, technique, and results. *Endocr Rev* 1982; 3 (3): 245–279.
- Thomas L.** Parathyroid hormone (PTH). *Clinical Laboratory Diagnosis*. TH-Books, Frankfurt. 1st English edition 1998: 248–250.
- Azari R, Passler Ch, Kaczirek K, Scheuba Ch, Niederle B.** Hypoparathyroidism after total thyroidectomy. *Arch Surg* 2008; 143 (2): 132–137.
- Cavicchi O, Piccin O, Caliceti U et al.** Accuracy of PTH assay and corrected calcium in early prediction of hypoparathyroidism after thyroid surgery. *Otolaryngol-Head Neck Surg* 2008; 138: 594–600.
- Roh JL, Park CI.** Intraoperative parathyroid hormone assay for management of patients undergoing total thyroidectomy. *Head Neck* 2006; 28 (11): 990–997.
- Alonso MD, Lopez JDS, Pena MI et al.** Serum PTH levels as a predictive factor of hypocalcemia after total thyroidectomy. *CIR ESP* 2009; 85 (2): 96–102.
- McLeod IK, Arciero C, Noordzij JP et al.** The use of rapid PTH assay in predicting postoperative hypocalcemia after total or completion thyroidectomy. *Thyroid* 2006; 16 (3): 259–265.
- Grodski S, Farrell S.** Early postoperative PTH levels as a predictor of hypocalcemia and facilitating safe early discharge after total thyroidectomy. *Asian J Surg* 2007; 30 (3): 178–182.
- Fahmy FF, Gillett D, Lolen Y et al.** Management of serum calcium level in post-thyroidectomy patients. *Clin Otolaryngol* 2004; 29: 735–739.
- Pasielka JL.** What is new in General Surgery: Endocrine Surgery. *J Am Coll Surg* 2004; 199: 437–445.
- Thomusch O, Machens A, Sekulla C, Ukkat J, Brauckhoff M, Dralle H.** The impact of surgical technique on the postoperative hypoparathyroidism in bilateral thyroid surgery: a multivariate analysis of 5846 consecutive patients. *Surgery* 2003; 133: 180–185.
- Payne RJ, Hier MP, Tamilia M, McNamara E, Young J, Black MJ.** Same day discharge after total thyroidectomy. The value of 6 hour serum parathyroid hormone and calcium levels. *Head Neck* 2005; 27: 1–7.
- Soon PSH, Magarey Cj, Campbell P, Lalaludin B.** Serum Intact Parathyroid Hormone as a predictor of hypocalcemia after total thyroidectomy. *ANZ J Surg* 2005; 75: 977–980.
- Sands N, Young J, MacNamara E, Black MJ, Tamilia M, Hier MP, Payne RJ.** Preoperative parathyroid hormone levels as a predictor of postthyroidectomy hypocalcemia. *Otolaryngol Head Neck Surg* 2011; 144 (4): 518–521.
- Sahmkow SI, Audet N, Nadeau S, Camiré M, Beaudion D.** Outpatient thyroidectomy: safety and patient's satisfaction. *J Otolaryngol Head Neck Surg* 2012; 41 Suppl 1: S1–S12.

Received June 3, 2012.
Accepted October 27, 2013.