Hypocalcemia – the most common complication after total thyroidectomy

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Abstract: Objective: 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 histopathology 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 regaarding 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, histopathology final diagnosis, number of parathyroid glands identified during surgery, duration of surgery, surgeon’s experience, duration of hospital stay) and hypocalcemia after total thyroidectomy.
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 polygactin 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.

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 (Elecys 2010, Roche Diagnostics, Mannheim, Germany) was used. Normal laboratory ranges of iPTH set by our laboratory were 15–65 pg/ml (16). Normal laboratory ranges of sCa set by our laboratory were 2.0–2.6 mmol/l, clinically significant 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 defined hypoparathyroidism as iPTH<15 pg/ml (iPTH bellow 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).

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 thyrotoxicosis. 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 α=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 (0.13) 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-
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 because 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 limits 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.

<table>
<thead>
<tr>
<th>iPTH</th>
<th>Hypocalcemia</th>
<th>Normal Ca.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (iPTH&lt;15)</td>
<td>30</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Normal (iPTH≥15)</td>
<td>12</td>
<td>72</td>
<td>84</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>73</td>
<td>115</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>iPTH</th>
<th>With symptoms</th>
<th>Without symptoms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (iPTH&lt;15)</td>
<td>22</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Normal (iPTH≥15)</td>
<td>0</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>93</td>
<td>115</td>
</tr>
</tbody>
</table>

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 symptom 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 symptom 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