PROGNOSTIC SIGNIFICANCE OF INTRAOPERATIVE PTH TEST FOR THE DEVELOPMENT OF POST-THYROIDECTOMY HYPOCALCAEMIA

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ABSTRACT
The high incidence of postoperative hypoparathyroidism after total thyroidectomy and the significant morbidity associated with it can account for the sustained efforts to find reliable, affordable markers for the prognosis of this condition. Therefore, a lot of attention has been paid recently to the perioperative measurement of the parathyroid hormone (PTH) as an immediate indicator showing the parathyroid glands functional status. There are a lot of studies in the relevant literature demonstrating that PTH is a highly sensitive marker, with high specificity to predict development of postoperative hypocalcemia. Recent studies analyze in-depth not only the absolute values of PTH, but also the dynamics of its levels during surgery. The number and timing of sampling for testing is a matter of discussion. Importance is attached also to the hormone testing methods. Research results determine intraoperative PTH (IOPTH) as a valuable additional test for early risk assessment of hypocalcaemia allowing prevention and timely treatment of patients at risk. Early identification of risk groups of patients creates a real opportunity to reduce the incidence of this complication by autotransplantation of parathyroid glands. Despite the encouraging results the predictive accuracy of this indicator is not 100%, which requires careful result interpretation. The findings of researchers are not uniform, probably due to differences in study design, the methods used in PTH testing, and the accepted reference range of serum calcium. This impedes comparison of data and highlights the need for similar analyzes in each specialized center.

Key words: thyroidectomy, hypocalcaemia, parathyroid hormone

INTRODUCTION
The high incidence of postoperative hypoparathyroidism after total thyroidectomy and the significant morbidity associated with it are the reason why there are sustained efforts to find reliable and affordable prognostic markers for this condition. A lot of attention has, therefore, been paid recently to the perioperative measurement of the parathyroid hormone (PTH) as an immediate indicator showing the parathyroid glands functional status. There are a lot of studies in the relevant literature demonstrating that PTH is a highly sensitive marker, with high specificity to predict development of postoperative hypocalcemia. Recent studies analyze in-depth not only the absolute values of PTH, but also the dynamics of its levels during surgery. The number and timing of sampling for testing is a matter of discussion. Importance is attached also to the hormone testing methods.

Intraoperative monitoring of PTH involves a series of procedures of taking and treating biological material during surgery with subsequent measurement of PTH by specialized express methods (described below). These highly sensitive methods provide results within a few minutes and give valuable information about the functional status of the parathyroid glands before closure of the operative field. This in turn can motivate important decisions including autotransplantation of parathyroid glands to prevent hypocalcemia in the postoperative period.1

IOPTH AS A PROGNOSTIC FACTOR FOR POSTOPERATIVE HYPOCALCAEMIA
The first description of the express intraoperative PTH monitoring was made in 1988.2 In the following decades, the method has been further elaborated...
and studied and has now established itself as a reliable marker of radical surgery in the surgical treatment of primary hyperparathyroidism.\textsuperscript{3-5} The short half-life of PTH, the ability to accurately and quickly determine its values, and its leading role in assessing the postoperative calcium status and phosphate metabolism motivate a number of analyzes of its importance for prognosis and prevention of hypocalcemia after thyroid resections. For example, in a prospective study of Alia P, et al. including 52 patients with thyroidectomy, the authors indicate that postresection PTH levels below 1.9 pmol/l and relative decline in its value by 62.5% provides 90% sensitivity and 97.9% specificity in assessing the risk of hypocalcemia in the postoperative period.\textsuperscript{6}

In this analysis, the incidence of hypoparathyroidism in patients with thyroidectomy is 38% and is significantly higher than in the cases with partial resection of the thyroid gland. Other researchers have published similar results. Chindavijak has found that PTH levels measured 20 min after removal of the gland are significantly lower in hypocalcaemic patients.\textsuperscript{7} The author points out that 17 of 19 patients with PTH <15 pg/ml have developed hypocalcaemia compared with the 3 of 11 patients with PTH > 15 pg/ml. The mean intraoperative level of PTH in normocalcaemic patients was 24.7 pg/ml, while in the group of patients with low serum calcium it was 9.2 pg/ml. The difference is statistically significant.

Threshold value of PTH associated with higher risk of hypocalcaemia varies in the different researches. For example, Lam et al. found that all patients with a PTH ≤ 8 pg/ml one hour after thyroidectomy subsequently developed hypocalcaemia requiring treatment, and all patients with PTH ≥ 9 pg/ml after surgery remained normocalcaemic.\textsuperscript{8} These results highlight PTH as a prognostic indicator with 100% sensitivity and specificity. Summarized data on the predictive significance of PTH are presented in the meta-analysis of 12 studies conducted by Noordzij et al.\textsuperscript{9} The results of 457 patients with thyroidectomy were analyzed - 21.1% of these developed hypocalcaemia after surgery. The mean intraoperative PTH level measured between 0 and 20 min after removal of the gland is significantly lower in hypocalcaemic patients (10.66 ± 13.56 pg/ml) compared with the patients who remained normocalcaemic after surgery (34.24 ± 24.16 pg/ml). The authors do not find significant differences in pre-operational levels of PTH in both patient groups.

Although there is much evidence that patients developing hypocalcaemia have lower intraoperative PTH levels, the use of this indicator has some limitations. They are related to the individual characteristics of the calcium-phosphate metabolism and preoperative PTH values and hamper the interpretation of specific serum concentrations measured in the intraoperative period. Therefore, most researchers adopt as more important prognostic factor the relative decline in PTH related to baseline values prior to surgery.\textsuperscript{6,10,11} For example, in a study of Alia et al. the postoperative PTH levels for normocalcaemic patients were lower by 41.5% on average than the baseline values compared with the levels in the patients who have developed hypocalcaemia (80.5%).\textsuperscript{6} A PTH decrease by 62.5% is defined by the authors as the threshold value with the highest sensitivity and specificity.\textsuperscript{6} Higgins et al. find that the decrease in PTH by 75% from baseline 20 minutes after thyroidectomy has the highest predictive value.\textsuperscript{10} Similar threshold value (75.7%) is obtained by Di Fabio et al. in a study of 81 patients with thyroidectomy.\textsuperscript{12} Analysis of their results takes into account the fact that the average decrease in PTH is more pronounced after thyroidectomy (53%) compared to cases with unilateral lobectomy (20%) which is consistent with the significantly lower incidence of postoperative hypoparathyroidism after partial thyroid resections.\textsuperscript{12} The abovementioned meta-analysis of Noordzij et al. states that the a decrease in PTH by 65% compared to preoperative levels measured 1 to 6 hours after thyroidectomy has a 96.45% sensitivity and 91.4% specificity for the development of hypocalcemia.\textsuperscript{9} The different threshold levels of PTH decline provided in individual studies are most likely related to differences in the methods of PTH measurement, accepted reference ranges of calcium and the design of studies.\textsuperscript{13-15} This defines the need for obtaining individual values based on data from own analyses in each specialized center.\textsuperscript{6,14,8}

The issue of the number and the time of sampling for intraoperative measurement of PTH is widely discussed in the literature.\textsuperscript{14,16-18} This problem is analyzed in detail regarding the surgical treatment of hyperparathyroidism.\textsuperscript{3,4} There are currently no accepted consensus recommendations for the period after thyroidectomy in which IOPTH has the highest predictive value.\textsuperscript{10} In the quoted study of Chindavijak et al. PTH level at 20 min after removal of the gland has a positive predictive value of 89.5% and negative predictive value of 72.7% for the development of hypocalcemia.\textsuperscript{7} In the study design of Fabio et al. a 10-minute interval after thyroidectomy is selected and the results also confirm the high predictive value of IOPTH.\textsuperscript{12} After
repeated follow-up of PTH at 0, 2, 4, 6, 24 and 48 hours after surgery Lombardi et al. find that hormone values below the lower limit (<10 pg/ml) at 4 and 6 hours predict most correctly hypocalcaemia with 100% specificity and 94% sensitivity. Sywak et al. tested PTH at 4 and 24 hours following a thyroidectomy in 100 patients and found that for an accurate prediction of hypocalcaemia a single test at 4 hours is sufficient. In a study including 201 patients with thyroidectomy Vescan et al. compare the levels of PTH measured 1 hour after surgery with those reported on the following morning. The comparison makes the conclusion that the results are comparable and the values of one-hour-postoperative PTH accurately select patients at higher risk for hypocalcaemia. The high predictive value of early PTH measurements is confirmed in a study by Roh and Park, who compare hormone levels 10 minutes, 1 hour and 24 hours after surgery. Hypocalcaemia was developed by 34 of the 92 patients and they are reported to have significantly lower PTH levels 10 minutes after thyroidectomy. The authors find that the results at 10 minutes significantly correlate with subsequent measurements and can be used as a prognostic factor for postoperative hypoparathyroidism. The high predictive potential of PTH, measured immediately after thyroidectomy and the correlation with the levels in the later hours, is linked by some researchers to the short half-life of PTH. 

Despite the promising results of the aforementioned studies, the prognostic value of PTH is not accepted unequivocally by all authors. For example, Ghaheri et al. in a post-thyroidectomy study of 80 patients conclude that postoperative PTH levels correlate with hypocalcaemia, but they cannot predict it. After an original study of Lombardi et al., the same authors published follow-up data analysis on 523 post-thyroidectomy patients, 199 (38%) of whom have developed hypocalcaemia. The authors find normal PTH levels 4 hours after thyroidectomy in 70 patients who have subsequently developed hypocalcaemia, as 11 of them had significant subjective symptoms. In conclusion they agree that the use of PTH alone does not accurately predict postoperative clinically significant hypocalcaemia. Del Rio et al. evaluated the predictive value of PTH in 1006 patients 24 hours after thyroidectomy. Hypocalcaemia was developed by 253 patients while in 152 patients the complication was manifested within the first 24 hours. Out of the remaining 101 patients with late onset of hypocalcaemia only 49 had low PTH. As a result, the authors do not accept PTH at 24 hours as a prognostic factor. A review of four contemporary studies published by the Australian Endocrine Surgeons finds that 7% of patients with normal PTH develop mild self-limiting hypocalcaemia not requiring the application of vitamin D and intravenous calcium supplements. The opinion of the authors is that normal PTH levels accurately predict post-thyroidectomy normocalcaemia allowing early and safe hospital discharge but the prognostic potential of low PTH levels is weak.

**CLINICAL AND LABORATORY METHODS FOR IOPTH MONITORING**

Given the great scientific interest, a significant number of methods for rapid intraoperative measuring of PTH have been developed recently. Various semiautomatic and automatic analyses with an acceptable performance period for intraoperative use are known - QuiCk-IntraOperative Intact PTH (Nichols Institute Diagnostics), Turbo Intact PTH (Diagnostic Products Corporation), STAT-I0-I-PTH (Future Diagnostics), QuiCk-IntraOperative Bio-Intact PTH (Nichols Institute Diagnostics), Elecsys PTH (Roche Diagnostics). Rapid intraoperative methods are primarily designed to measure intact PTH and can evaluate aminoterminal truncated PTH fragments (like 7-84). A method for rapid intraoperative measurement of bio-intact PTH has also been designed (1-84). A questionnaire survey of Hortin and Carter among 92 respondents finds that 47% of the surveyed professionals used the intraoperative Turbo Intact PTH (IMMULITE) method, 33% - QuiCk-IntraOperative Intact PTH, 7% - Elecsys PTH, 13% - another method. All these methods possess the accuracy needed by the goals of intraoperative monitoring. Comparative studies show good correlation between the express and routine methods for PTH testing. In addition, direct comparative analyses among intraoperative tests do not show the advantages of a particular express method in regard to the final results.

**PRACTICAL IMPORTANCE OF IOPTH MONITORING**

Routine measurement of PTH in the postoperative period is an important prognostic risk indicator of hypocalcaemia and may induce prophylactic administration of calcium and prolongation of hospital stay. In contrast, rapid IOPTH test offers a real opportunity to reduce the incidence of this complication by autologus grafting of parathyroid glands through early identification of risk patients. The effectiveness of this approach is analyzed in the study of Barczyński et al.
study involves a group of 170 patients indicated for thyroidectomy whereas parathyroid autologous grafting is carried out selectively in cases of identified IOPTH <10 ng/L. Review of the results does not identify cases with sustained hypoparathyroidism among the studied patients and the incidence of transient hypocalcaemia is 11.2%. Furthermore, the authors report that the transitional hypoparathyroidism is significantly more frequent in routine autologous parathyroid grafting in all patients without the use of IOPTH as a leading factor (22.4%). Increased risk of transient hypocalcaemia after parathyroid autologous grafting (associated with the resection and parathyroid devascularisation) is reported elsewhere.12,27 That is why, according to Di Fabio et al., routine autologous grafting is not warranted but it is indicated when either the vitality of the parathyroid glands is questionable or upon registration of drop in IOPTH by 75% compared with preoperative levels. The authors summarize the role of IOPTH in thyroidectomy in the following areas: 1) identifying low-risk patients enables early and safe hospital dismissal; 2) helps to avoid unnecessary treatment with calcium and vitamin D preparations; 3) It is another objective method to assist the surgeon in the evaluation of parathyroid function and decision making for autologous grafting to prevent sustained hypoparathyroidism.12

Cost-effectiveness of IOPTH monitoring

The results of the cited studies motivate further economic analyses to assess the appropriateness of routine use of IOPTH in surgical practice. According to Lam et al. an easily accessible and yet reliable test for the selection of patients requiring close monitoring and calcium supplementation and of those suitable for early hospital dismissal would significantly reduce health costs.8 Higgins et al. note that the cost of IOPTH is much lower than the costs associated with longer hospital stay.10 McHenry reports that surveillance under 23 hours leads to 56% cost reduction compared with 48-hour hospitalization for patients indicated for thyroidectomy.28 Given that IOPTH provides valuable information enabling timely calcium supplementation for patients at risk and early hospital discharge of low-risk patients, its introduction into routine practice is justified and economically viable.26,29,30

Conclusions

In conclusion, postoperative hypoparathyroidism is the most common complication after thyroidectomy. Its manifestation is associated with significant morbidity, long hospital stays and high treatment costs. In the literature IOPTH is defined as a valuable complementary test to make an early assessment of the risk for hypocalcaemia, thus allowing prevention and timely treatment of patients. Despite the encouraging results this indicator cannot yield 100% accurate prognostic prediction, which makes the careful interpretation of the results quite necessary. The researchers arrive at different conclusions, probably due to the differences in the study designs, the methods they use in PTH testing and the accepted reference ranges of serum calcium. This renders any comparison of data difficult and highlights the need for such analyses in each specialized center.

References

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ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ИНТРАОПЕРАТИВНОГО ПТГ ТЕСТА ДЛЯ РАЗВИТИЯ ГИПОКАЛЬЦИЕМИИ ПОСЛЕ ТИРЕОИДЭКТОМИИ

М. Али

РЕЗЮМЕ

Высокая частота постоперативного гипофункции после тиреоидэктомии и значительная степень заболеваемости, связанная с ним, являются поводом для продолжительных усилий с целью установления надежных и в то же время доступных прогностических маркеров его развития. В связи с этим в последние годы большое значение приобретает интраоперативное измерение паратиреоидного гормона (ПТГ) в качестве непосредственного показателя, отражающего функциональное состояние паращитовидных желез.

В литературе имеется множество исследований по проблеме, указывающих на ПТГ как на маркер с высокой чувствительностью и специфичностью при предсказании гипокальциемии во время постоперативного периода. В современные исследования углубленному анализу подвергаются не только абсолютные стоимости ПТГ, а также и динамика в его уровнях во время оперативного вмешательства. Вопрос дискусию представляют число и время взятия пробы для исследования. Значение приобретает методика исследования гормона.

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Результаты исследований определяют интраоперативный ПТГ (ИОПТГ) как ценный дополнительный тест ранней оценки риска гипокальциемии, позволяющей проводить соответствующую профилактику и своевременное лечение рисковых пациентов.

Ранняя идентификация рисковых контингентов создает реальную возможность для снижения частоты этого осложнения посредством проведения аутотрансплантации паращитовидных желез. Несмотря на обнадеживающие результаты прогностическая точность этого показателя меньше 100%; следовательно внимательная интерпретация результатов является необходимостью.

Заключения исследователей неоднозначны, что по всей вероятности объясняется различиями в дизайне исследований, различиями в применяемых методах исследований ПТГ, в принятых референтных границах сывороточного кальция. Это затрудняет сопоставление данных и подчеркивает необходимость в проведении подобных анализов в каждом специализированном центре.