

## CLINICAL STUDY

# Measurement of intact parathormone during operation for primary hyperparathyroidism

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## ABSTRACT

In this prospective study, the role of the intact parathormone (iPHT) levels for the verification of pathologic parathyroid tissue removal during parathyroidectomy, was analyzed in 441 patients diagnosed with primary hyperparathyroidism. The level of intact parathormone was obtained before the initial incision (baseline level) and 10 minutes after the pathologic parathyroid gland removal (control value). In 80 % of cases, the decrease of intact parathormone was more than 50 % of the baseline level. The comparison of preoperative and postoperative intact parathormone levels can also be used as marker of parathyroid hyperplasia or persistent hyperparathyroidism. This method is necessary mainly for performance of focused, miniinvasive approaches as well as in reoperations. This method is of significant benefit in cases of negative preoperative examination methods. The determination of intact parathormone level increases the success of parathyroidectomy (Ref. 26). Text in PDF [www.elis.sk](http://www.elis.sk).  
KEY WORDS: primary hyperparathyroidism, intact parathormone, parathyroidectomy, surgery, human.

## Introduction

Primary hyperparathyroidism is one of the most common endocrine conditions. PHPT is being diagnosed with increasing frequency mainly as the result of the introduction of routine serum calcium measurements. The cause of the primary hyperparathyroidism is a hyperfunction of one or more parathyroid glands, caused by adenoma, hyperplasia or rarely, a carcinoma. Clinically, it represents a disorder of calcium, phosphate and bone metabolism, often leading to biochemical, renal and bone syndrome. Patients with primary hyperparathyroidism significantly more often suffer from gastroduodenal ulcers, pancreatitis or cholecystolithiasis than normal population (Broulik et al, 2011, 2015). Other disorders, such as: muscle weakness or neuropsychiatric diseases can occur as well. Moreover, hypercalcaemia negatively influences the heart and blood circulation. Primary hyperparathyroidism can be also asymptomatic, at least in initial stages. The diagnosis is based on finding the hypercalcaemia, hypophosphataemia and increased level of parathormone in serum. Moreover, these patients have an increased activity of alkaline phosphatase, hypercalciuria and hyperphosphaturia.

In case of a clear diagnosis, a surgical treatment, based on the removal of the pathologically changed parathyroid tissue, is indicated (Naňka et al, 2006). Preoperatively, maximum effort to localize particular parathyroid tissue, most often by sonography or scintigraphy, is necessary (Libánský et al, 2008). Surgical treatment, parathyroidectomy, is definitive, curative and relatively safe. During the operation, the main goal is to remove the proper pathologic parathyroid tissue (Libánský et al, 2008). The success of pathologic parathyroid gland removal is verified by histology or, nowadays, more often by an intact parathormone (iPHT) level measurement (Schneider et al, 2014, Irvin et al, 2004). In case of an experienced surgeon, preoperative or postoperative complications are rare and mortality rate is very low. Major postoperative complications include paresis of the recurrent laryngeal nerve or persistent postoperative hypocalcaemia (Adánek et al, 2005). A persistent hyperparathyroidism represents an important complication as well. In order to prevent it the level of intact parathormone measurement during the operation has been recommended (Schneider et al, 2014, Irvin et al, 2004).

## Material and methods

Together, 481 patients were operated for primary hyperparathyroidism in the Third Department of Surgery in Motol Hospital, Prague, between January 2012 and January 2015. In 441 of them, who were included into this prospective study, the level of intact parathormone was measured during the operation. Inclusion criteria were set as: (i) patient with the preoperative diagnosis of primary hyperparathyroidism, (ii) patient indicated for parathyroidectomy, (iii) patient operated in the Department of Surgery in Motol Hospi-

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tal, Prague and (iv) patient with a complete documentation during the preoperative, operative and postoperative period. Patients who did not match all inclusion criteria were excluded from the study.

All surgeries were performed in general anaesthesia. Bilateral neck exploration was done, as described previously (Adámek et al, 2005). In brief, on neck, collar skin incision followed by midline incision and in some cases, partial sternotomy, videothoracoscopy or video-assisted mediastinoscopy was performed (Libánský et al, 2016 a,b). Superficial neck fascia was cut in midline, infrahyoid muscles pulled laterally, lobes of the thyroid gland were detached from surrounding structures and pulled medially. Both recurrent laryngeal nerve and inferior thyroid artery were identified. Close to the site of crossing of recurrent laryngeal nerve and inferior thyroid artery, majority of parathyroid glands were found. If not, they were identified in other regions, where ectopic parathyroid tissue might occur, in relation to preoperative localization methods and results of our previous anatomical study (Naňka et al, 2006).

The first blood sample was taken before the incision. The level of intact parathormone obtained, served as a baseline level, as recommended by Irvin et al (2004) and Kaczirek et al (2005). Second blood sample was taken 10 minutes after the pathologic parathyroid gland was removed. When the decrease of intact parathormone was more than 50% of the original value, this measurement was taken as diagnostic for the proper parathyroid gland removal, i.e. the surgical success (Prager et al, 2003, Riss et al, 2013). All samples were analyzed in the Department of Clinical Biochemistry, Second Faculty of Medicine and Teaching Hospital Motol, Prague, employing laboratory machine Roche Cobas e411 with a specific kit for the statim iPTH measurement. In our laboratory, the reference values for intact parathormone were set as 1–7 pmol/L (10–65 pg/mL). The success of the operation was set as a decrease of total calcium levels in 48 hours after surgery.

All values are reported as the mean±S.E.M. Statistical significance ( $p<0.05$ ) between intact parathormone levels before and after the operation was compared using the paired Student's *t*-test ( $p<0.05$ ).

## Results

During past three years, together 882 blood samples in 441 patients were successfully examined and the levels of intact parathormone measured. From these 441 patients, 376 (85.26 %) were females and 65 (14.74 %) were males. The mean age of patients was 60.52±8.25 years. From this sample, 119 patients (26.98 %) had renal syndrome, 203 patients (46.03 %) had bone syndrome, 31 patients (7.03 %) had gastroduodenal ulcer, 9 patients (2.04 %) had pancreatitis, 110 patients (24.94 %) had cholecystolithiasis, 44 patients (9.98 %) suffered from psychiatric disorders, 238 patients (53.97 %) had arterial hypertension and only 49 patients (11.11 %) had no signs of other disease in their medical history. The mean value of total calcium before the operation was 2.76±1.11 mmol/L, the mean value of intact parathormone before the operation was 19.53±11.48 pmol/L.

The mean level of intact parathormone before the incision was 19.72±12.45 pmol/L (range 1.77–222.2 pmol/L). The mean value of intact parathormone after the operation was 6.50±4.98 pmol/L (range 0.74–50.85 pmol/L; in one case 156.5 pmol/L – see be-

low). This difference has been significant ( $p<0.05$ ). In 354 cases (80.27 %), the decrease of intact parathormone was more than 50 % of the original value. In 85 cases (19.27 %), the intact parathormone level decreased as well, but not more than 50 %. In two cases (0.45 %), even an increase of intact parathormone was observed; however, in all these 87 cases (19.73 %), the total calcium levels decreased significantly. In 13 cases (2.95 %), the level of intact parathormone was originally below 6 pmol/L, so any significant decrease could have not been found. In four cases (0.91 %), no significant decrease of intact parathormone and calcium levels was found. In one case, the parathyroid carcinoma was found. This patient was re-operated afterwards. In one patient, the preoperative level of intact parathormone was 159.5 pmol/L and postoperative value was 156.5 pmol/L. In this patient, the generalization of clavicular neuroendocrine carcinoma with positivity of parathormone in tumor cells was found during the operation. The decrease of calcium levels below 2.5 mmol/L after the operation were not found in 20 patients (4.54 %). From these, in 7 patients the calcium levels decreased in the following day, in one case there was a neuroendocrine tumor, in one case there was a parathyroid carcinoma.

Postoperative hypocalcaemia with paresthesia occurred in 87 cases (19.73 %), where the oral or intravenous calcium substitutes were administered. In two cases (0.45 %), the patient was re-operated. In one case (0.23 %), due to a severe general health status, the reoperation was contraindicated. During the postoperative period, no permanent hypocalcaemia was found. The drain was removed in the mean 1.88±0.95 postoperative day. Patients were released home in day 2.86±1.98.

## Discussion

Women were affected significantly more often than men (ratio 5.8 : 1), which is in accordance with other studies (Broulík et al, 2011, Miller et al, 2008). The sampling of blood for the analysis of intact parathormone levels is currently used as a marker whether the pathologically changed parathyroid tissue was removed (Riss et al, 2007 b, 2009). The decrease in parathyroid hormone level during operation was most predictive of cure of primary hyperparathyroidism (Davis et al, 2013). Preoperative measurement of intact parathormone levels and their comparison can prevent the unfortunate leaving of pathologically changed parathyroid gland in the body of the patient. Moreover, the persistent parathyroid hyperplasia can be prevented. In our sample, together three patients have persistent hypercalcaemia, from which one had parathyroid carcinoma and one neuroendocrine clavicular carcinoma.

The success of the operation with the intact parathormone level measurement was 99.10 %. When compared to previous years, this modification increased the success of the operation for 0.50 % (Adámek et al, 2005). For the measurement of intact parathormone, different criteria exist (Barczynski et al, 2009). The blood sample is taken before the surgical incision and after the parathyroid gland removal (Riss et al, 2007a). Some authors report the association of intraoperative parathormone level over 4.24 pmol/mL with an increased risk of persistence and recurrence in primary hyperparathyroidism (Rajaei et al, 2015). The persistence

of an increased intact parathormone has been reported to occur in 8–40 % of cases. For example, Wang et al (2005) reports that to occur in 15 % of cases. The persistence of increased parathormone level can be caused by vitamin D insufficiency as well. The injection of furosemid stimulates PTH secretion in healthy adults (Muller, 2015). The measurement of peroperative intact parathormone levels should be performed during minimally invasive approaches on parathyroid glands (Joliat et al, 2015). This method is associated with a significant decrease of (i) operation time, (ii) length of hospitalization, and (iii) occurrence of complications including not esthetic scarring (Adámek et al, 2005, Libánský et al, 2007). Some authors propose the financial benefit of the approach (Barczynski et al, 2009), whereas others doubt it (Stalberg et al, 2006). The use of intact parathormone monitoring decreases the occurrence of postoperative hypercalcaemia and accelerates healing of the patient after the operation (Bergenfelz et al, 2009). Some authors propose that the level of preoperative intact parathormone positively correlate with the volume of pathologically changed parathyroid tissue and thus easier identification of scintigraphy is proposed (Biertho et al, 2004). Increased level of peroperative intact parathormone indicates a higher probability of persistent primary hyperparathyroidism (Schneider et al, 2014).

The determination of intact parathormone level during the operation can be used as a marker of proper pathologic parathyroid tissue removal. Such operation should be performed in specialized centers, equipped with devices necessary for quick and routine intact parathormone level measurements.

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Received May 4, 2016.

Accepted January 4, 2017.