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Parathormone concentration in the fluid of fine-needle parathyroid biopsy for assessing the effectiveness of surgical treatment of patients with primary hyperparathyroidism

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Abstract

Introduction: The aim of the work was to evaluate the usefulness of intraoperative determination of parathyroid hormone (PTH) concentration in the fluid of fine-needle biopsy lesions of pathologically parathyroid glands for their identification and evaluation of the effectiveness of surgical treatment of primary hyperparathyroidism (PHP).

Material and methods: The study group comprised 75 patients: 65 women and 10 men, aged 33–78 years (mean 57.5), operated in the years 2019–2020 due to PHP. Seventy-nine biopsies of fine-needle aspiration lesions were assessed intraoperatively as pathological parathyroid glands were collected, and the concentration of PTH was determined in their lavage fluid. The results were compared with a control group of 20 patients operated at that time for various forms of goitre, without concomitant parathyroid disease.

Results: In 79 biopsies, the presence of the parathyroid gland was confirmed 72 times. The concentration of PTH in the biopsy fluid exceeded the value of 5000 pg/mL 70 times, 1 was 3733 pg/mL, and 1 was 1985 pg/mL. Seven times (8.9%), the biopsy was for a colloid nodule instead of the parathyroid gland. The concentration of PTH in the fluids of these biopsies was low and ranged from 5.3 to 500 pg/mL. In the control group, the concentration of PTH in postoperative thyroid biopsies was low and did not exceed the reference value range of up to 64 pg/mL. Comparison of the results of the study group with the control group shows significantly higher PTH values in parathyroid biopsies compared to biopsies of thyroid specimens ($p = 0.017$), with a sensitivity of 100% and a specificity of nearly 93%.

Conclusions: Intraoperative determination of PTH concentration in the fluid of fine-needle biopsy lesions with diseased parathyroid glands allows for their identification and evaluation of the effectiveness of surgical treatment of PHP. Testing the concentration of PTH in the biopsy fluid of dissected parathyroid glands is characterized by high sensitivity and specificity of the method. The value of PTH concentration in fluid from parathyroid biopsies does not depend on the cause of PHP (*Endokrynol Pol* 2022; 73 (4): 706–711)

Key words: primary hyperparathyroidism; parathyroid gland; parathyroidectomy; fine-needle biopsy; intraoperative parathyroid hormone

Introduction

Primary hyperparathyroidism (PHP), due to disturbances in regulatory mechanisms, feedback of parathyroid hormone (PTH) secretion and calcium-phosphate metabolism leads to extremely severe systemic metabolic complications and gradual destruction of the body [1, 2]. The course of the disease is initially secretive, and both the diagnosis of PHP and the identification of the diseased parathyroid gland in preoperative imaging studies are often difficult [3–5]. Diagnostic difficulties appear especially often with the coexistence of nodular changes in the thyroid gland and in the ectopic location of the pathologically

changed parathyroid gland. The lack of localization of the parathyroid gland responsible for the symptoms of the disease in preoperative imaging tests translates into difficulties with intraoperative identification, which may influence the effectiveness of surgical treatment [3].

The aim of the study is to assess the usefulness of intraoperative determination of PTH concentration in the fluid of fine-needle biopsy pathologically changed parathyroid glands for their identification and for evaluation of the effectiveness of surgical PHP treatment. The method we propose may complement the commonly used determination of PTH in peripheral blood serum.



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Material and methods

The study included 75 patients — 65 women and 10 men aged 33–78 years (mean 57.5) — treated surgically in the period from 01/01/2019 to 31/10/2020 due to PHP. Prior to the operation, all patients were tested for ionized calcium levels in peripheral blood serum, and the concentration of PTH was determined using an immunochemical method. Before the operation, the diseased parathyroid glands were located by MI-BI SPECT scintigraphy and ultrasound examinations. Seventy-nine lesions assessed intraoperatively as pathological parathyroid glands were removed. Immediately after excision, fine-needle aspiration biopsy of the specimens was performed. Biopsy samples were supplemented with saline (0.9% NaCl) to a volume of 1 cm³. In the fluid obtained in this way, the concentration of PTH was determined, and the results were related to the concentration of PTH in the blood serum.

Twenty minutes after resection of pathologically changed parathyroid glands, peripheral blood was collected for examination and the concentration of PTH in its serum was determined. The reduction of PTH levels in peripheral blood below 50% of the preoperative value proved the effectiveness of the surgical treatment. Excised lesions were assessed by two independent histopathologists.

The control group consisted of 20 patients (19 women and 1 man) aged 23–73 years (mean 48.6) operated at that time due to various forms of goitre, without concomitant disorders of calcium and phosphate metabolism and diagnosed parathyroid disease.

In these patients, the concentration of PTH was determined in a colloidal nodule of the thyroid excised during surgery.

Statistical analysis was performed using Statistica 13.1 software, with the calculation of arithmetic averages, standard deviation, application of the Wilcoxon test, and assessment of statistical variability. The sensitivity and specificity of the method were also assessed. A true positive result was a high PTH concentration in the biopsy fluid with histopathologically confirmed pathologically changed parathyroid gland, and a true negative result was a normal PTH concentration and no parathyroid tissue. A false positive result corresponded to elevated PTH values in the absence of parathyroid tissue in the biopsy, and a false negative result was a low PTH and parathyroid tissue in the biopsy.

Results

In all 75 patients undergoing the study who were operated on for PHP, the preoperative serum PTH concentration was elevated and ranged from 79 to 2042, mean 352.6; standard deviation (SD) 386.61 (n: 15–65) pg/mL, and the concentration of ionized calcium was 1.27–2.15, mean 1.61; SD = 0.21 (n: 1.12–1.32) mmol/L (Tab. 1).

Histopathological examination revealed the presence of a single parathyroid adenoma in 28 (37.3%)

Table 1. Characteristics of 75 patients subjected to the assessment of parathormone (PTH) concentration in the fluid of biopsies assessed microscopically as excised parathyroid glands

	Number (n = 75)		%
Age [years]	33–78 (57.5)		
Sex			
Male	10		13.3
Group of patients subjected to the test	65		86.7
Cause of primary hyperparathyroidism (PHP)			
Single change			
Hyperplasia (H)	28		37.3
Adenoma (A)	42		56.0
Multiple changes			
A + A	1		1.34
H + H	1		1.34
H + A	1	6.7	1.34
A + A + H	1		1.34
H + H + A	1		1.34
Parathyroid hormone (PTH) [pg/mL]			
Before operation	79–2042 (avg. 352.6)		
20 minutes after operation	3.3–220.6 (avg. 35.57)		
1 day after operation	2.09–86.5 (avg. 24.01)		
Ionized calcium levels in peripheral blood serum (ICA²⁺) [mmol/L]			
Before operation	1.27–2.15 (mean 1.61)		
0 day after operation	1.05–2.01 (mean 1.39)		
1 day after operation	0.96–1.98 (mean 1.25)		

A — adenoma; H — hyperplasia

Table 2. Assessment of parathormone (PTH) concentration in the fluid of biopsy specimens of postoperative material in patients with primary hyperparathyroidism (PHP) and nodular goitre

Tested biopates Hist-pat result	PTH value [pg/mL]	Study group				Control group	
		PHP (n = 79)		Colloid nodule of the thyroid gland (n = 20)			
		L 79	100%	L	100%		
Changed parathyroid							
	> 5000	72	70	91.1	88.6	0	0
	65 < PTH < 5000		2		2.5	0	0
Colloid nodule (absence of parathyroid)							
	> 65	7	2	8.9	2.5	0	0
	< 65		5		6.4	20	100

patients, in another 42 (56.0%) single gland hyperplasia, and in 5 (6.7%) multiple lesions.

The efficacy of surgical treatment, confirmed by the PTH concentration test in blood serum collected 20 minutes after resection of the pathologically changed parathyroid gland, was found in all 75 (100%) patients with PHP. In these patients, a decrease in PTH concentration in peripheral blood serum to the value of 3.2–220.6 pg/mL was noted (mean 36.52 pg/mL).

In the postoperative examination, a decrease in concentration of ionized calcium in peripheral blood serum was noted in all 75 patients to the value of 1.05–2.01 mmol/L, mean 1.39; SD = 0.25 on day zero after surgery and 0.96–1.98 mmol/L, mean 1.25; SD = 0.2 one day after surgery.

Out of 79 biopsies of postoperative material assessed macroscopically as an altered parathyroid gland, in 70 the concentration of PTH in the fluid of biopsies exceeded the value of 5000 pg/mL, which was the upper limit of diagnostic possibilities, 1 was 3733.0 pg/mL, and 1 was 1985 pg/mL (Tab. 2). In these cases, the histopathological examination of the biopsy material confirmed the presence of parathyroid hyperplasia or adenoma, and the type of parathyroid pathology had no effect on the PTH concentration in the biopsy fluid. The seven remaining biopsies (8.9%) were colloidal nodules with no parathyroid tissue present. The concentration of PTH in the fluid of these 5 biopsies was low and amounted to 5.3–21.4 pg/mL, mean 13.6, and twice the normal serum values of 158.4 and 500 pg/mL, respectively.

In the control group, no elevated PTH concentration values were found in the preoperative period, and its concentration was 15.6–66.4 pg/mL, mean 36.83; SD 14.04. There were also no pathological changes in the preoperative ionized calcium concentration in the blood serum, the value of which ranged between 1.1 and 1.27 mmol/L, mean 1.20; SD 0.04. The concentration of PTH in postoperative thyroid biopsies in these patients was low and did not exceed the range of

normal values in the blood serum, at 1.2–11.9 pg/mL, mean 5.69; SD 4.38. In the postoperative period, 1 day after surgery, the concentration of PTH in the peripheral blood serum was 1.20–62.6 pg/mL, mean 26.96; SD 19.11 and Ca^{2+} + 0.99–1.21 mmol/L, mean 1.13; SD 0.06.

A comparison of the study group with the control group shows significantly higher PTH values in parathyroid biopsies compared to those of colloidal thyroid nodules ($p = 0.017$). Analysis of the PTH results in the fluid of postoperative specimens of both the study group with primary hyperparathyroidism and the control group with nodular goitre was used to assess the sensitivity and specificity of the method used (Tab. 3).

The sensitivity of the method, calculated on the basis of the obtained results, was 100%, and its specificity was 92.6%. The usefulness of the method used to identify the pathologically changed parathyroid gland is proven by a high positive predictive value of 97.3%.

Discussion

Surgical treatment of PHP with excision of pathologically changed parathyroid glands is considered to be the most effective method of treating the disease, significantly exceeding 90% efficacy, allowing for permanent relief of its symptoms and effective cure. A number of pre-, intra-, and postoperative factors play an important role in achieving such good results [1, 6].

The type of parathyroid pathology, the duration of the disease, and the resulting clinical condition of patients as well as the presence of metabolic changes in many systems, including nephrological, cardiovascular, digestive, articular, and nervous system loads, have a significant impact on the further course of the disease [2].

The effectiveness of surgical treatment largely depends on the preoperative imaging diagnostics of the parathyroid glands. Its result allows the surgeon to obtain as much detailed information as possible on

Table 3. Assessment of the sensitivity and specificity of the parathormone (PTH) usefulness test in the fluid of biopsy specimens of postoperative material to identify pathologically changed parathyroid glands

Test result	Condition		Predictive value
	Positive	Negative	
Positive	TP ↑ PTH + parathyroid tissue 72	FP ↑ PTH + no parathyroid tissue 2	Positive 97.3%
	FN ↓ PTH + parathyroid tissue 0	TN ↓ PTH + no parathyroid tissue 25	Negative 100%
Sensitivity 100%		Specificity 92.6%	
Accuracy of the test 98%			

TP — truly positive; FP — false positive; FN — false negative; TN — truly negative

the number and location of the diseased parathyroid glands, including the ectopy of their location, but it is never completely certain [3, 5, 7].

Technetium-99m methoxyisobutylisonitrile single-photon emission computed tomography/computed tomography (^{99m}Tc-MIBI SPECT/CT) scintigraphy is a highly effective imaging method in the diagnosis of PHP. In everyday practice, a commonly available and useful examination is ultrasound examination of the neck, which allows the visualization of pathologically changed parathyroid glands. There are reports of the use of ultrasound images to perform targeted fine-needle aspiration biopsy (FNAB) of the parathyroid glands along with cytological evaluation of biopsies and PTH levels within them [8–11]. However, we believe that when qualifying patients for parathyroid FNAB, one should remember about possible complications or limitations of this method [12, 13]. These include the presence of a haematoma and the appearance of local inflammation with the formation of an abscess. The possibility of an iatrogenic implant in the pathway after the biopsy of parathyroid cells, including neoplastic cells, should be clearly emphasized. Because transplantation of parathyroid cells into adjacent tissues and their further proliferation (parathyroidism) may later cause surgical treatment failure and result in recurrence of the disease symptoms, the authors of the article do not recommend its use.

However, the preoperative imaging assessment of the parathyroid glands does not always allow for a certain determination of the location of the altered glands, and the final result of the operation depends largely on the experience and knowledge of the surgeon [14]. Localization difficulties may be caused by the ectopic location of the parathyroid glands or the presence of goitre and the coexistence of nodular changes in

the thyroid gland, requiring simultaneous preoperative diagnostic procedures [5, 15, 16]. The course of the disease, concomitant burdens, and the general condition of the operated patients require the surgeon to perform an effective and quick surgical procedure [17–20].

The presence of nodular changes within the thyroid gland should additionally be an indication for simultaneous thyroid surgery. This approach is even more appropriate in the case of multiple endocrine neoplasia syndromes with close coexistence of parathyroid and thyroid pathologies [6, 16, 18].

The surgeon's experience and the correct macroscopic assessment of the altered parathyroid glands still largely determine the final outcome of the operation. A commonly accepted criterion that determines the effectiveness of the treatment undertaken is a significant decrease by at least 50% in the level of PTH in the peripheral blood serum 20 minutes after excision [20–24]. According to the experience of the authors and the results of the conducted research, the significantly high concentration of PTH in the biopsy fluid of resected parathyroid glands, compared to the concentrations in the peripheral blood before the procedure, confirms their identification, and, together with the results of preoperative imaging studies supporting a single lesion as the cause of PHP, it may prove the effectiveness of operation. Performing a parathyroid biopsy immediately after its excision also prevents the implantation of cells of the pathologically changed parathyroid gland, including cancer cells, in the operating field, which can lead to early relapse of the disease. In addition, the time of anaesthesia and surgery devoted to waiting for the PTH results in peripheral blood after parathyroidectomy is reduced. Taking into account the often-severe clinical condition of patients, it is extremely important.

Low PTH values in the biopsy fluid, no significant decrease, or an increase in PTH level in the peripheral blood serum should be indications for the surgeon for extended exploration of the neck and a further search for the cause of the disease (6, 16, 25, 26). One should also remember about the possibility of the coexistence of multiple adenomas, which, if left, reduce the effectiveness of surgical treatment and lead to persistent hyperparathyroidism. The result of the operation may be determined by the insufficient extent of the operation in cases of multiple hyperplasia.

As it results from the analysis of the obtained results and their comparison with the results of the histopathological examination of the obtained material, no statistically significant differences were found in the values of PTH in the fluid from biopsies depending on the type of parathyroid pathology that was the cause of PHP. High sensitivity and specificity indicate the usefulness of examining the concentration of PTH in the fluid of biopsies from excised parathyroid glands to assess the effectiveness of the applied surgical treatment.

Performing a biopsy during surgery is not technically difficult and does not require additional equipment, and good cooperation with the hospital laboratory allows for a quick result. The high value of PTH in the performed biopsies provides the basis for effective differentiation between the parathyroid gland and thyroid nodules in doubtful situations and is the main advantage of the method used. In conjunction with the intraoperative macroscopic evaluation of the punctured gland and the compliance of its location with preoperative imaging tests, it may also prove the effectiveness of the treatment applied and allow for faster completion of the procedure. The final confirmation of the effectiveness of the applied surgical treatment is obtained by determining the level of PTH in the peripheral blood serum after the procedure.

Conclusions

Intraoperative determination of PTH concentration in the fluid of fine-needle biopsy lesions with diseased parathyroid glands allows for their identification and evaluation of the effectiveness of surgical treatment of PHP.

Testing the concentration of PTH in the biopsy fluid of dissected parathyroid glands is characterized by high sensitivity and specificity of the method.

The value of the PTH concentration in fluid from parathyroid biopsies does not depend on the cause of PHP.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Statements of ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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