Urina M., Palamarchuk V., Tovkai O., Kuts V., Yuzvenko T. Laboratory criteria for the persistence of secondary hyperparathyroidism in patients with chronic kidney disease. Journal of Education, Health and Sport. 2020;10(11):69-81. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2020.10.11.007
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.11.007
https://zenodo.org/record/268459

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 16.10.2020. Revised: 30.10.2020. Accepted: 12.11.2020.

LABORATORY CRITERIA FOR THE PERSISTENCE OF SECONDARY HYPERPARATHYROIDISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE

M. Urina[1], V. Palamarchuk[1], O. Tovkai[1], V. Kuts[1,2], T. Yuzvenko[1]

[1]Ukrainian Scientific and Practical Center for Endocrine Surgery, Transplantation of Endocrine Organs and Tissues Health Ministry of Ukraine, Kyiv
[2]State organization "National institute of phthisiology and pulmonology named after F.G. Yanovsky National academy of medical sciences of Ukraine", Kyiv

Abstract

Secondary hyperparathyroidism is a complication of chronic kidney disease in both the non-dialysis and dialysis stages. Even modern advances in drug therapy cannot change the fact that most CKD patients require surgical treatment. The purpose of the treatment of SHPT is to normalize mineral metabolism, prevent bone diseases and prevent extraosseous manifestations. One of the methods of surgical treatment is subtotal parathyroidectomy. Persistence or recurrence of the disease occurs in 5-30% of cases.

Purpose of the study. To determine laboratory criteria for the persistence of SHPT in patients with chronic kidney disease on the second day after parathyroidectomy.

Materials and methods. The study involved 118 patients with end-stage CKD with prolonged renal replacement therapy. All patients had clinical and laboratory signs of secondary hyperparathyroidism. In the period from 2009 to 2019, patients underwent subtotal parathyroidectomy. The patients were divided into two groups. This division was based on the presence of persistence or recurrence of the disease. The main group included 20 patients with

laboratory signs of SHPT persistence; the comparison group included 98 patients without signs of disease's persistence.

Results. Analysis of changes in laboratory parameters in patients with persistence and in patients without signs of disease's persistence revealed certain differences in their postoperative level. In all 118 cases, there was a significant decrease in PTH in the postoperative period - from 31.5 to 99.6%. Using ROC-analysis, a study was carried out of the possibility of using the degree of PTH reduction as a predictor of the persistent course of SHPT and the optimal cut-off thresholds were established. A decrease in the postoperative level of PTH by 90.9% or more indicates an effective PTE. The maximum value of the test specificity (1.000 (0.968; 1.000)) is achieved when the PTH reduction is 76.0%. At the same time, the maximum value - 1.000 (0.968; 1.000) - reaches the predictive value of a positive test result.

Conclusions. Using the subtotal parathyroidectomy in our study, the persistent of SHPT occurred in 16.9% of cases. A decrease in PTH levels on the second day after surgery less than 76% comparatively to the preoperative level should be considered as a predictor of the development of disease persistence. A reduction in PTH of more than 90.9% may be an indication of sustained remission.

Key words: Parathyroid gland; parathyroid hormone; secondary hyperparathyroidism; chronic kidney disease; persistence of secondary hyperparathyroidism.

INTRODUCTION

Secondary hyperparathyroidism (SHPT) is inevitable complication of chronic disease of kidneys, both on non-dialysis and on the dialysis stage. Even modern achievements in the field of medicine therapy cannot influence on circumstance that most patients with chronic kidneys disease (CKD) need surgical treatment, namely, parathyroidectomy (PTE) [1, 2].

In accordance with recommendations of KDIGO2017 a parathyroidectomy is recommended to the patients with SHPT regardless of the stage of process at presence of resistance to medicine therapy [3]. The aim of treatment of SHPT is normalization of mineral metabolism, prophylaxis of diseases of bones and prevention of extra-skeletal disease [4, 5]. A choice of volume of surgery in case of SHPT is a debatable issue and depends on further tactics of treatment. [6].

One of them there is a subtotal parathyroidectomy that assists the improvement of quality and lengthening of patient's lives [7, 8].

Taking into account the severe somatic condition of this category of patients and undesirability of the repeated interventions, the warning of persistence or recurrent of disease and postoperative hypoparathyroidism acquires especial significance. But according to the literature data, the persistence of the disease appears in 5-30% of cases.

The reasons of these states can be: inadequate PTE, supernumerary and ectopic PTG, that were not educed on the stage of the preoperated topical diagnostics, hyperplasia of residual tissue of PTG [9 - 12]. It is well known that the criteria of successful parathyroidecomy in case of PHPT is an inoperative decline of the parathyroid hormone (PTH) by more than 50% from the preoperated level [13, 14]. Conformities of PTH's decline in case of SHPT have not been completely studied. Till now there are no clear predictive criteria of SHPT's persistence.

According to literature the intraoperative decline of PTH on 80-90% testifies to the effectively conducted parathyroidectomy for patients with CKD [15 - 17]. At the same time, a cost of intraoperative monitoring of PTH is high enough, and this limits its wide use both in our country and all over the world [18, 19].

With the purpose of improvement of efficiency of surgical treatment of patients with SHPT and decline of amount of persistence and resistance of process the level of PTH and dynamics of its decline were analysed in a postoperated period.

The aim of the study is to determine the laboratory criteria of persistence of SHPT for patients with the chronic kidney disease on the second twenty-four hours after a parathyroidectomy.

MATERIALS AND METHODS

The retrospective research was provided on the base of the Ukrainian research and practice centre of endocrine surgery, transplantation of endocrine organs and tissues, Health Ministry of Ukraine, Kiev.

118 patients with the terminal stage of CKD, clinical and laboratory signs of secondary hyperparathyroidism (SHPT) were included in our research. The mean age of the patients was 48,0 ± 1,2 (min - 21, max - 76), among them women - 64 (54,2%), men - 54 (45,8 %). The leading disease that became a reason of chronic kidney insufficiency and development of SHPT in the investigated group of patients was a chronic glomerulonephritis. The amount of patients that were on hemodialysis - 108, on a peritoneal dialysis - 10.

Presented correlations of patients, that were on hemodialysis and peritoneal dialysis, accordingly, 91,5 % and 8,5 %. The middle term of hemodialysis was 13,3 ± 0,4, to the peritoneal dialysis - 11,4 ±1,9.

All patients had complaints of main disease, which in most cases were associated with the osteoarticular and cardiovascular system. Between the 2009 and the end of 2019 a subtotal parathyroidectomy was provided for all patients with the subsequent division of them into two groups.

In the basis of this distribution was a fact of persistence of disease. A basic group was entered by 20 patients with the laboratory signs of persistence of SHPT, in the group of comparison - 98 patients without the signs of persistence of disease.

In basic group the persistence of the disease took place in 15 (75%) cases, recurrence of disease - in 5 (25%) cases. The reasons of the reoperations were: recurrence from the residual glandular tissue in 5 (25%) cases, persistence took a place in 15 (75%) cases and was caused by supernumerary PTG in 6 (40%) and ectopic adenomas of PTG in 9 (60%) cases.

The topical diagnostics was carried out using an ultrasound Toshiba NEMIO (Japan) and 64-slice computed tomography Toshiba Aquilion CX (Japan).

Laboratory researches. The examination included mandatory determination of preoperative and postoperative levels of PTH, total calcium, ionized calcium, phosphorus. Determination of serum PTH was performed by enzyme-linked immunosorbent assay using the ACCESS immunochemical system (automatic analyzer and all consumables have the same name), manufactured by BECKMAN COULTER USA.

Statistical analysis. Data were collected and processed using MS Excel 2013. The statistical analysis program StatPlus 7 was used to perform the calculations. To compare the series of independent observations that did not comply with the normal distribution law, the Mann-Whitney test was used. MedCalc v.19 and StatPlus 7 were used for ROC analysis.

Operational characteristics of diagnostic tests were calculated according to generally accepted formulas. They were determined by the Tukey method when diagrams were being constructed in the “box”- “mustache” type.

RESULTS

In patients with SHPT associated with CKD values of PTH significantly exceed the reference values (normal 15-65 pg / ml). For this group of patients, PTH range from 150 pg/ml to 300 pg/ml [20].

The level of parathyroid hormone, total and ionized calcium, phosphorus was determined in all patients in the preoperative stage and on the second day after surgery. The results of laboratory parameters are shown in table 1.

Table 1

The preoperated levels of laboratory indexes are in a group (n=118)

Laboratory indicator	Median, Me (Q_1; Q_3)	Reference value (target value)
PTH (pg/ml)	1897,5 (1434,3; 2568,5)	15 – 65 (150-300)
Common calcium (mmol/l)	2,50 (2,35; 2,64)	2,25 – 2,65
Ionized calcium (mmol/l)	1,22 (1,13; 1,29)	1,15 – 1,32
Phorphorus (mmol/l)	2,09 (1,80; 2,46)	0,87 – 1,45

Analysis of changes in laboratory parameters in patients with (n = 20) and without (n = 98) signs of disease persistence revealed certain differences in their postoperative level, although before surgery no statistically significant differences were observed (Table 2, Figure 1).

Table 2

Dynamics of the postoperative changes of laboratory indexes in groups with persistence and without persistence of the disease

The group of patients without persistence of the disease (n=98)		
Laboratory indicator	Median, Me (Q_1; Q_3) / max – min value	
	Before the operation	After the operation
PTH (pg/ml)	1880,1 (1441,0; 2566,0) / 833,0-5000,0	89,0 (63,5; 122,3)*## / 8,0-374,0
Common calcium (mmol/l)	2,54 (2,36; 2,63) / 1,95-3,08	2,40 (2,29; 2,50)*#/ 1,50-2,80
Ionized calcium (mmol/l)	1,22 (1,13; 1,29) / 0,95-1,76	1,02 (0,87; 1,15)*/ 0,56-2,38
Phorphorus (mmol/l)	2,17 (1,80; 2,50) / 1,41-3,89	1,77 (1,45; 2,01)* / 0,98-3,22
The group of patients with signs of persistence of the disease (n=20)		
Laboratory indicator	Median, Me (Q_1; Q_3) / max – min value	
	Before the operation	After the operation
PTH (pg/ml)	2136,0 (1365,0; 2565,5) / 955,0-4975,0	282,5 (193,3; 384,0)* / 74,0-918,0
Common calcium (mmol/l)	2,43 (2,31; 2,64) / 2,07-2,90	2,23 (2,00; 2,40)* / 1,50-2,50
Ionized calcium (mmol/l)	1,17 (1,08; 1,33) / 0,92-1,61	0,98 (0,85; 1,15)* / 0,68-1,32
Phorphorus (mmol/l)	2,07 (1,84; 2,18) / 1,54-3,03	1,72 (1,45; 1,89)* / 0,98-2,65

Notes:
1. * it is a difference of index with a level to the operation statistically meaningful ($p<0,001$);
2. # - a difference between groups is statistically meaningful ($p<0,01$);
3. ## - a difference between groups is statistically meaningful ($p<0,001$).

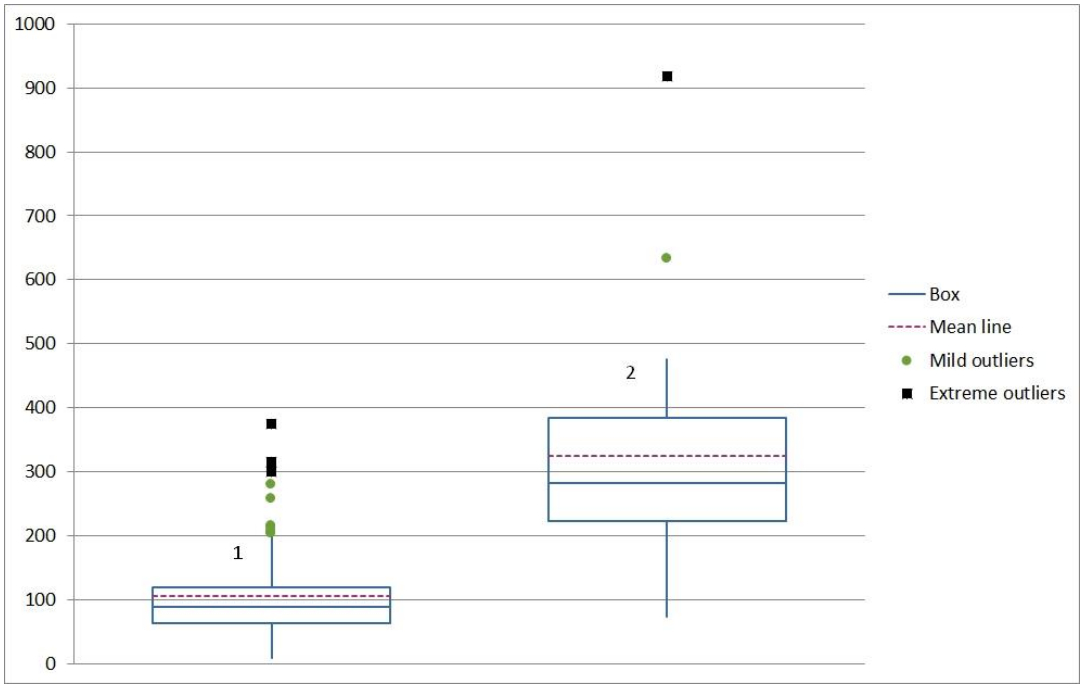

Fig.1. Comparison of postoperative parathyroid hormone levels in groups of patients with persistence and without persistence of the disease

Notes:
- 1- comparison group, 2 main groups
- the difference between the indicator and the level before the operation was statistically significant ($p < 0.001$).

Table 2 and Figure 1 show a high significant difference ($p < 0.001$) in PTH levels in patients with no signs of persistence - 89.0 (63.5; 119.3) and those in whom they were subsequently detected - 282.5 (222.0; 384.0) pg / ml.

This prompted us to investigate the possibility of using parathyroid hormone levels as a predictor of persistent SHPT.

To solve this problem, we used the method of ROC analysis with the construction of the ROC curve shown in Fig.2.

The sensitivity of the test is 95.0% and the specificity is 78.6%. Such results are achieved when the value of PTH = 135 pg / ml selected as the cut-off threshold. This provides an overall diagnostic efficiency (DE), i.e. the percentage of correct diagnoses, 79.7%.

Analysis of the dynamics of changes in the level of PTH after surgery compared with the preoperative level revealed the following. In all 118 cases there was a significant decrease in PTH - from 31.5 to 99.6%. In the vast majority of patients (77.1%) this decrease exceeded 90%, while among such patients there were only 4 (20.0%) cases of persistence. And at decrease in PTH more than 92,3% - persistence has not been noted at all. Comparison of the

intensity of PTH reduction and the frequency of complications suggested the existence of a connection between these events: the smaller the relative reduction of PTH, the greater the risk of complications (Fig. 3).

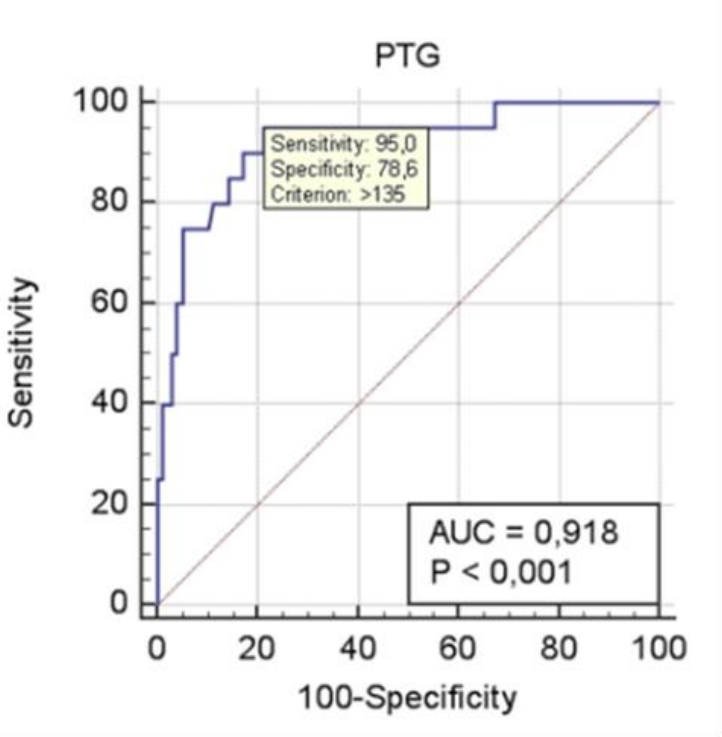

Fig.2. ROC curve for postoperative PTH

The high value of the area under the ROC curve - 0.918 (95% CI: 0.853; 0.961) - indicates the high quality of the proposed model.

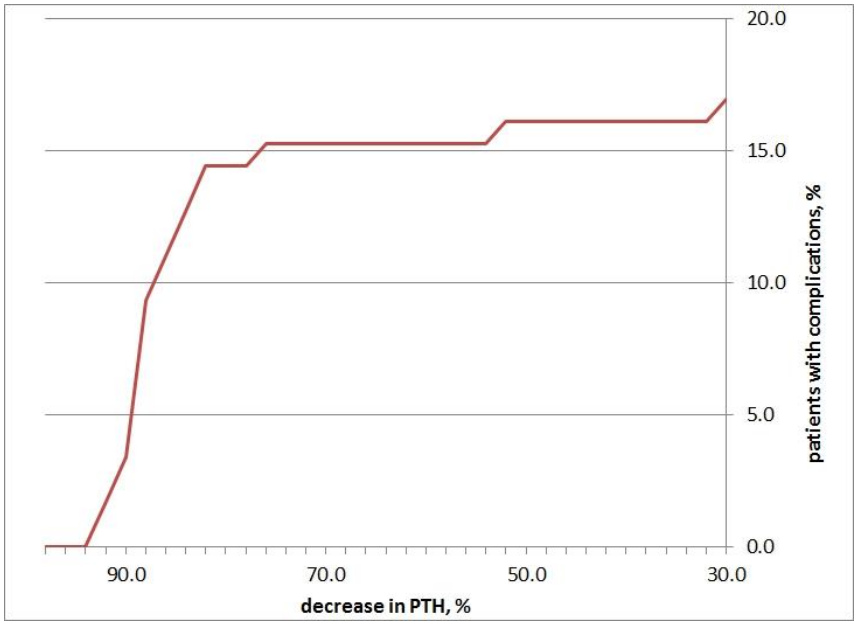

Fig. 3. Change in the accumulated frequency of complications depending on the intensity of PTH reduction

In order to determine the possibility of using the value of the relative reduction of PTH as a predictor of disease persistence and the establishment of acceptable cut-off thresholds, we performed the appropriate ROC-analysis procedures, the results of which are shown in Fig.4.

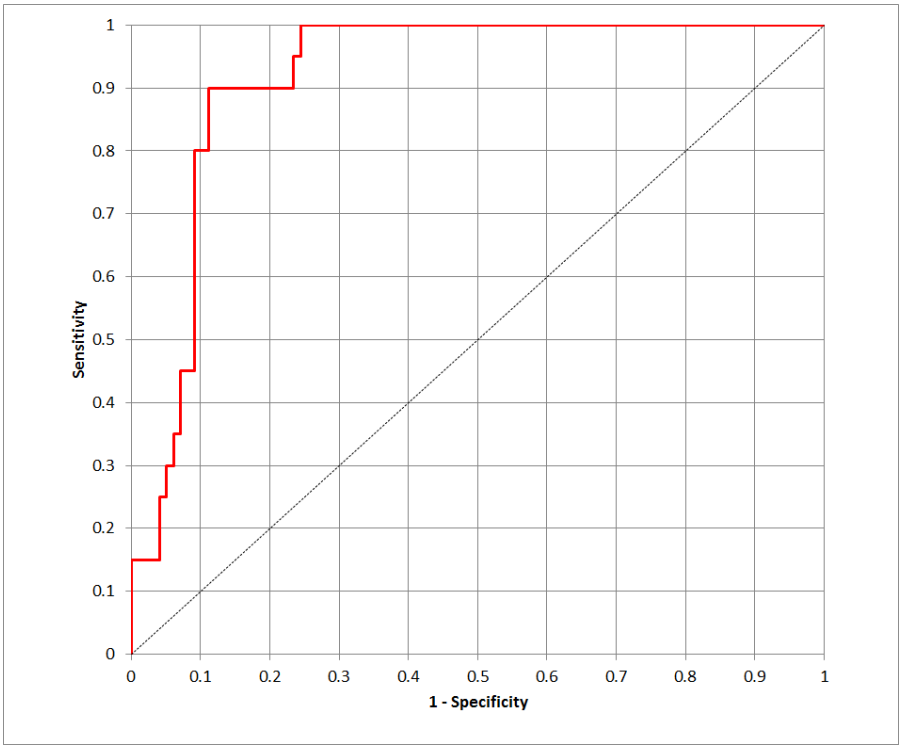

Fig.4. ROC curve for postoperative PTH

A positive result of the test was considered to identify a patient with persistence when reaching a certain threshold, the value of reducing the intensity of PTH reduction.

The high value of the area under the ROC curve - 0.916 (95% CI: 0.865; 0.967) indicates the high quality of the proposed model. The Yuden index is also quite high - 0.788.

The sensitivity of the test is 90.0% and the specificity is 88.8%. Such results are achieved with the selected cut-off threshold of 90.9%.

From our point of view, the most revealing is the indicator of specificity, the graph of changes which depending on the chosen cut-off threshold (% reduction of PTH) is presented in Fig.5.

The graph clearly shows that the maximum value of specificity (1,000 (0,968; 1,000)) is reached at the value of the change in PTH of -76.0% and remains so throughout the range of values that were observed. At the same time, the prognostic significance of a positive test result reaches the maximum value - 1,000 (0.968; 1,000).

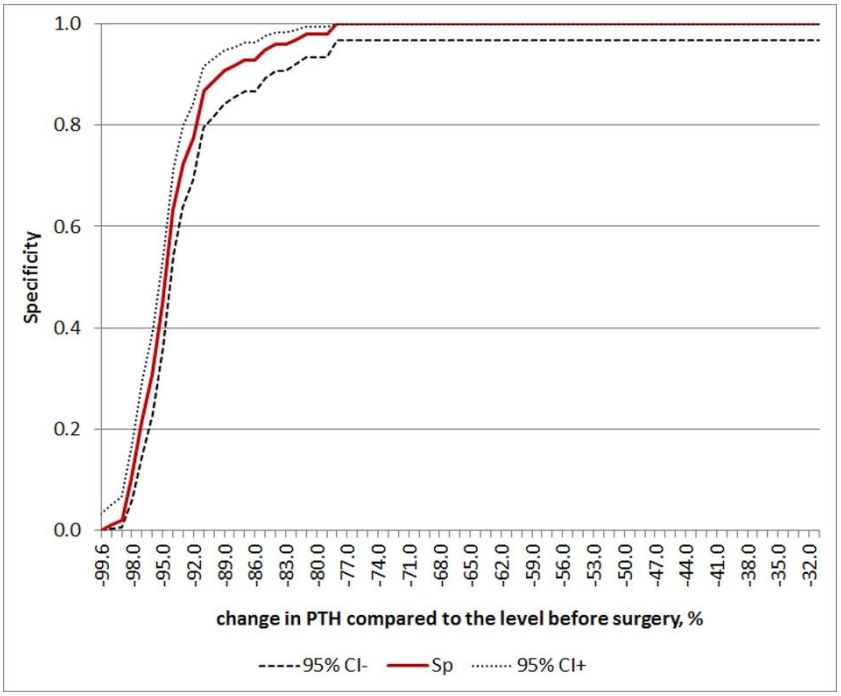

Fig.5. Graph of test specificity with 95% confidence interval

Note: dotted lines indicate the 95% confidence interval

Although, by definition, specificity (Sp) expresses the probability of a negative result in a subject without disease, and positive prognostic value (PPV) characterizes the ability of the test to correctly predict the presence of disease in a subject with a positive result, such results can be viewed, interpreted as follows: receiving after surgery a reduction in PTH levels by less than 76% should be considered a serious warning about the possibility of persistence of the disease in such a patient.

DISCUSSION

If in the case of PHPT parathyroidectomy is the gold standard of treatment and in most cases leads to complete cure of patients, in the case of SHPT on the background of CKD - is only one stage of multicomponent therapy helps to improve biochemical parameters and positively affect the bone system. [4, 25].

Persistence and recurrence of the disease can occur in both PHPT and SHPT. The high percentage of persistence of HPT is due to the peculiarities of embryonic development and migration of the parathyroid glands (PSH), individual variability in the number of thyroid gland, the quality and completeness of preoperative topical diagnosis, the experience of the endocrine surgeon.

According to the results of our study, the persistent course of the disease occurred in 16.9%. This result is quite good, as according to the literature, the persistence and recurrence of SHPT occurs in 25-30% of cases [10, 21, 22].

To assess the effectiveness of surgery, the determination of the intraoperative level of PTH has been used for a long time. For decades, the authors have been trying to determine a clear time interval and gradient for the reduction of PTH concentrations, which may indicate the success of surgery. The advantages of determining the intraoperative PTH level in the case of PHPT have been very well studied. A 50% decrease in the intraoperative PTH level relative to its preoperative level indicates a successful parathyroidectomy [14].

But these approaches cannot be used in the case of SHPT in dialysis patients [23].

According to modern scientific studies, the optimal percentage of intraoperative reduction of PTH after PTE in patients with CKD is in the range from 50% to 90% for 5-20 minutes after removal of the altered glands [24]. The clearance of PTH in SHPT has its own characteristics: the rapid intraoperative fall is a further gradual decrease in the postoperative stage (unlike PHPT), so it is difficult to predict the final level of PTH.

The above, as well as the high cost of intraoperative PTH monitoring was the basis for determining the level of PTH on the second day after PTE in our study.

In this study, postoperative PTH reduction of more than 90.9% indicated effective parathyroidectomy and occurred in 98 (83.0%) cases. In 20 (16.9%) cases of disease persistence, the PTH level decreased by less than 76%.

CONCLUSIONS

Using the subtotal parathyroidectomy in our study, the persistent of SHPT occurred in 16.9% of cases.

A decrease in PTH levels on the second day after surgery less than 76% comparatively to the preoperative level should be considered as a predictor of the development of disease persistence. A reduction in PTH of more than 90.9% may be an indication of sustained remission.

REFERENCES

1. Quarles LD, Berkoben M. Management of secondary hyperparathyroidism in dialysis patients. In: UpToDate. Available from: https://www.uptodate.com/contents/management-of-secondary-hyperparathyroidism-in-dialysis-patients (accessed on Mar 5, 2018).

2. Quarles LD, Berkoben M. Management of secondary hyperparathyroidism in adult nondialysis patients with chronic kidney disease. In: UpToDate. Available from: https://www.uptodate.com/contents/management-of-secondary-hy-yperparathyroidism-in-adult-nondialysis-patients-with-chronic-kidney-disease (accessed on Mar 5, 2018)

3. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int 2017; 92:26.

4. Springer International Publishing Switzerland 2017 B.C. Stack, Jr., D.L. Bodenner (eds.), Medical and Surgical Treatment of Parathyroid Diseases. DOI 10.1007/978-3-319-26794-4_1

5. Sarah Tomasello. Secondary Hyperparathyroidism and Chronic Kidney Disease. Diabetes Spectrum 2008 Jan; 21(1): 19-25. DOI:10.2337/diaspect.21.1.19

6. Parathyroidectomy in the Management of Secondary Hyperparathyroidism: Clin J Am Soc Nephrol. 2018 Jun 7; 13(6): 952–961. DOI: 10.2215/CJN.10390917.

7. Mier MV, Rodríguez M. Parathyroidectomy in dialysis patients: Indications, methods, and consequences. Semin Dial. 2019; 32:444–451. DOI:10.1111/sdi.12772

8. Mira Milas: Parathyroidectomy in end-stage kidney disease. In UpToDate, edited by Carty SE, Chen W, Waltham, MA, UpToDate Inc. Accessed October 25,2017

9. Monique Nakayama Ohe, Rodrigo Oliveira Santos and co. Intraoperative PTH cut-off definition to predict successful parathyroidectomy in secondary and tertiary hyperparathyroidism. DOI: 10.5935/1808-8694.20130088

10. Jun Yang Persistent secondary hyperparathyroidism caused by parathyromatosis and supernumerary parathyroid glands in a patient on haemodialysis BMC Nephrology volume 21, Article number: 257 (2020). DOI:10.1186/s12882-020-01917-3

11. Schneider R, Waldmann J, Ramaswamy A, Fernandez ED, Bartsch DK, Schlosser K. Frequency of ectopic and supernumerary intrathymic parathyroid glands in patients with renal hyperparathyroidism: analysis of 461 patients undergoing initial parathyroidectomy with bilateral cervical thymectomy. World J Surg. 2011;35:1260–5. DOI: 10.1007/s00268-011-1079-6.

12. Mario Cozzolino and co. Treatment of secondary hyperparathyroidism: the clinical utility of etelcalcetide. Ther Clin Risk Manag. 2017; 13: 679–689. DOI: 10.2147/TCRM.S108490

13. Gasparri, G., Palestini, N., Freddi, M., Sisto, G., & Camandona, M. (2016). Parathyroid Exploration for Primary Hyperparathyroidism. Primary, Secondary and Tertiary Hyperparathyroidism, 117–132. DOI:10.1007/978-88-470-5758-6_1

14. Modern Parathyroid Surgery and Intra-Operative Hormone Monitoring; Present Status, Future Concepts DOI: 10.4172/2157-7536.1000190

15. Monique Nakayama Ohe, Rodrigo Oliveira Santos and co. Intraoperative PTH cutoff definition to predict successful parathyroidectomy in secondary and tertiary hyperparathyroidism. DOI: 10.5935/1808-8694.20130088

16. Subtotal parathyroidectomy for secondary renal hyperparathyroidism: a 20-year surgical outcome study Langenbecks Arch Surg. 2016; 401(7): 965–974.
DOI:10.1007/s00423-016-1447-7

17. Melih Kara Evaluation of Intraoperative Parathormone Measurement for Predicting Successful Surgery in Patients Undergoing Subtotal/ Total Parathyroidectomy Due to Secondary Hyperparathyroidism The Laryngoscope 120(8):1538-44, August 2010. DOI: 10.1002/lary.21023

18. The Value of Intraoperative Parathyroid Hormone Monitoring in Localized Primary Hyperparathyroidism: A Cost Analysis Lilah F. Morris Ann Surg Oncol. 2010 Mar; 17(3): 679–685. DOI:10.1245/s10434-009-0773-1

19. Shawky et al., J Steroids Horm Sci 2018, 9:1 Modern Parathyroid Surgery and Intra-Operative Hormone Monitoring; Present Status, Future Concepts Journal of Steroids & Hormonal Science DOI: 10.4172/2157-7536.1000190

20. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42(4 Suppl 3):S1-201.

21. Dotzenrath C, Cupisti K, Goretzki E, Mondry A, Vossough A, Grabensee B, et al. Operative treatment of renal autonomous hyperparathyroidism: cause of persistent or recurrent disease in 304 patients. Langenbecks Arch Surg 2003;387:348-54.
DOI: 10.1590/S0102-86502007000200005

22. Gomes EMS, Nunes RC, Lacativa PGS, Almeida MH, Franco FM, Leal CTS, Patrício Filho PJM, Farias MLF, Gonçalves Ectopic and extranumerary parathyroid glands location in patients with hyperparathyroidism secondary to end stage renal disease. Acta Cir Bras. 2007 Mar-Apr;22(2). DOI:10.1590/S0102-86502007000200005

23. James W Moor 1, Steven Roberts : Intraoperative parathyroid hormone monitoring to determine long-term success of total parathyroidectomy for secondary hyperparathyroidism. Head Neck 2011 Mar;33(3):293-6. DOI: 10.1002/hed.21441

24. Monique Nakayama Ohe, Rodrigo Oliveira Santos: Intraoperative PTH cutoff definition to predict successful parathyroidectomy in secondary and tertiary hyperparathyroidism. Braz J Otorhinolaryngol, 2013 Aug; 79(4):494-9. DOI: 10.5935/1808-8694.20130088.

25. Urina M., Palamarchuk V.: Study of the correlation between the size of the parathyroid adenoma and the level of parathyroid hormone, calcium, phosphorus and vitamin D in the serum of patients with primary hyperparathyroidism. Clinical endocrinology and endocrine surgery, №2(2019). DOI: http://doi.org/10.30978/CEES-2019-2-30