

Early postoperative parathormone sampling and prognosis after total parathyroidectomy in secondary hyperparathyroidism

Dosagem pós-operatória precoce de paratormônio e prognóstico, após paratireoidectomia total por hiperparatireoidismo secundário

Authors

Climério Pereira do Nascimento Júnior¹
 Marília D'Elboux Guimarães Brescia¹
 Melani Ribeiro Custódio¹
 Ledo Mazzei Massoni Neto¹
 André Albuquerque Silveira¹
 Patrícia Taschner Goldenstein¹
 Sérgio Samir Arap¹
 Vanda Jorgetti¹
 Rosa Maria Affonso Moyses¹
 Fábio Luiz de Menezes Montenegro¹

¹ Universidade de São Paulo.

Submitted on: 8/19/2016.
 Approved on: 12/2/2016.

Correspondence to:

Climério Pereira do Nascimento Júnior.
 Universidade de São Paulo.
 Av. Dr. Enéas de Carvalho Aguiar, nº 255, Cerqueira César, São Paulo, SP, Brazil.
 CEP: 05403-000
 E-mail: climeriojr@yahoo.com.br

DOI: 10.5935/0101-2800.20170021

ABSTRACT

Introduction: There is possibility of a supernumerary hyperplastic parathyroid gland in dialysis patients after total parathyroidectomy and autograft in dialysis patients. **Objective:** To test if the early postoperative measure of parathyroid hormone (PTH) can identify persistent hyperparathyroidism. **Methods:** A prospective cohort of dialysis patients submitted to parathyroidectomy had PTH measured up to one week after operation. The absolute value and the relative decrease were analyzed according to clinical outcome of satisfactory control of secondary hyperparathyroidism or persistence. **Results:** Of 51 cases, preoperative PTH varied from 425 to 6,964 pg/mL (median 2,103 pg/mL). Postoperatively, PTH was undetectable in 28 cases (54.9%). In eight individuals (15.7%) the PTH was lower than 16 pg/mL, in 10 (19.6%) the PTH values were between 16 and 87pg/mL, and in five (9.8%), PTH was higher than 87 pg/mL. Undetectable PTH was more common in patients with preoperative PTH below the median ($p = 0.0002$). There was a significant correlation between preoperative PTH and early postoperative PTH (Spearman $R = 0.42$, $p = 0.002$). A relative decrease superior to 95% was associated to satisfactory clinical outcome. A relative decrease less than 80% was associated to persistent disease, despite initial postoperative hypocalcemia. **Conclusion:** Measurement of PTH in the first days after parathyroidectomy in dialysis patients may suggest good clinical outcome if a decrease of at least 95% of the preoperative value is observed. Less than 80% PTH decrease is highly suggestive of residual hyperfunctioning parathyroid tissue with persistent hyperparathyroidism, and an early reintervention may be considered.

Keywords: hyperparathyroidism, secondary; hypocalcemia; parathyroidectomy; parathyroid hormone; recurrence.

RESUMO

Introdução: Em pacientes renais crônicos dialíticos submetidos à paratireoidectomia total com autoenxerto, existe a possibilidade de uma glândula paratireoide hiperplásica residual. **Objetivo:** Verificar se a medida pós-operatória precoce do hormônio da paratireoide (PTH) após paratireoidectomia total com autoenxerto é útil para indicar uma glândula paratireoide residual ou supranumerária hiperplásica em pacientes dialíticos. **Método:** Em uma coorte prospectiva de pacientes em diálise submetidos a paratireoidectomia foi medido o PTH até uma semana após à operação. O valor absoluto e o decréscimo relativo foram analisados de acordo como desfecho clínico de controle satisfatório do hiperparatireoidismo ou persistência. **Resultados:** Em 51 casos, o PTH preoperatório variou entre 425 e 6.964pg/mL (mediana 2.103pg/mL). No pós-operatório, o PTH foi indetectável em 28 casos (54,9%). Em 8 indivíduos (15,7%), o PTH foi menor que 16pg/mL, em 10 (19,6%) os valores de PTH values estiveram entre 16 e 87pg/mL e em 5 (9,8%), o PTH foi superior a 87pg/mL. O PTH indetectável foi mais comum em pacientes com valor de PTH pré-operatório abaixo da mediana do PTH dos casos ($p = 0,0002$). Houve correlação significativa entre o PTH pré-operatório e o PTH pós-operatório precoce (Spearman $R = 0,42$, $p = 0,002$). Um decréscimo relativo superior a 95% associou-se a desfecho clínico satisfatório. O decréscimo relativo inferior a 80% associou-se à doença persistente, apesar de hipocalcemia inicial. **Conclusões:** A dosagem do PTH nos primeiros dias após à paratireoidectomia em pacientes dialíticos pode sugerir bom desfecho clínico quando há um decréscimo de pelo menos 95% em relação ao valor pré-operatório. O decréscimo inferior a 80% é indicativo de tecido paratireoideo residual com persistência do hiperparatireoidismo e uma reintervenção precoce pode ser considerada.

Palavras-chave: hiperparatireoidismo secundário; hipocalcemia; hormônio paratireoideo; paratireoidectomia; recidiva.

INTRODUCTION

Total parathyroidectomy with immediate heterotopic autograft is a well-recognized technique for the surgical treatment of severe secondary hyperparathyroidism (2HPT) in chronic kidney disease patients under dialysis.¹⁻³ Effective parathyroidectomy with significant reduction of parathormone (PTH) is associated to improvement in long-term survival.⁴

The aim of surgical treatment of 2HPT is improvement of the symptoms and the reduction of serum levels of calcium, phosphorus and PTH. If there is no improvement of the symptoms associated with elevated PTH levels within six months after parathyroidectomy, it is considered a persistence. If it occurs after six months, it is considered a recurrence.

The incidence of persistent 2HPT is about 4%.⁵ Persistence may be caused by a missed parathyroid (when less than four are found during surgery) or by a supernumerary gland. The recurrent 2HPT rate due to parathyroid autograft ranges from 20-60% in 10 years, increasing as time goes by.⁶ The recurrence rate in our patients who underwent surgery between 1987 and 2002 was about 15%. But comparison is not always easy since the recurrence criteria used in the literature are also not homogeneous.⁷

In patients in whom less than four parathyroid glands are found and excised, there is a high concern for possible persistence. As most individuals have four parathyroids, the identification and treatment of four glands is usually interpreted as a successful operation.

However, supernumerary parathyroid glands are commonly observed in patients with multiglandular parathyroid disease.⁸ Supernumerary glands may pass unnoticed during the operation and the clinical resolution of 2HPT may not ensue, after a four gland-parathyroidectomy. Conversely, both a missing fourth gland or a supernumerary parathyroid may be small and little functional, and control of 2HPT is still achieved, despite an apparently incomplete operation.⁹ Thus, the number of identified or excised glands is not a reliable marker of an adequate operation, if one considers the metabolic goals.

Postoperative hypocalcemia could suggest complete excision of all hyperfunctioning parathyroid tissue, but marked hypocalcemia requiring large amounts of calcium or calcitriol postoperatively may occur even when PTH levels are repeatedly high, probably due to hungry bone syndrome in severe or advanced cases of hyperparathyroidism.^{10,11}

Independent of postoperative hypocalcemia, which is highly driven by bone metabolism, the detection of significant levels of PTH may suggest persistence of a clinically significant parathyroid gland. We hypothesize that measuring PTH during the first days after an intended total parathyroidectomy may be a clinically interesting tool to predict persistent disease.

METHODS

In a prospective observational study approved by Institutional Review Board of patients with 2HPT undergoing an intended total parathyroidectomy (resection of at least four parathyroid glands) with immediate forearm autograft, in a single tertiary hospital (Internal registry number Cappesq 1368/06 and Certificado de Apresentação para Avaliação Ética 1133.0.015.000-06) PTH levels were sampled pre and postoperatively. These results were available for the present analysis, for persistent disease.

All patients signed an informed consent before inclusion. Patients operated on from 2008 to 2010 were included. Individuals with a functioning kidney graft were not included, as their metabolic profile is quite different from patients under regular dialysis.

Early PTH was defined as any sample obtained during the first week after the operation, in a vein not draining the autograft. Cases lacking any PTH measure during the first week after the operation were excluded. PTH was measured by IMMULITE 2000 (DPC and Siemens). At the time of observation the reference range of the method in normal individuals was 16 to 87 pg/mL. Normal range for serum calcium and phosphorus were 8.6-10.2 mg/dL and 2.7-4.5 mg/dL, respectively.

The number of patients with undetectable and detectable postoperative PTH and the correlation between preoperative and early postoperative values were analyzed. When PTH was detectable, stratifications according to reference ranges for the method were tested.

To test the possible value of PTH reduction as a prognostic marker, the clinical control of the disease was analyzed according to the relative reduction of PTH, calculated as follows: (Preoperative PTH - Early Postoperative PTH)/Preoperative PTH. We estimated the success of the operation according to this ratio.

Persistent 2HPT was considered when PTH levels were above than KDIGO targets, demonstrated at any time until six months after the operation. The KDIGO

work group to recommend two to nine times the upper normal limit for the assay used.¹² On the other hand clinical control of the disease was considered when PTH was within target levels at least until six months, without hypercalcemia, uncontrollable phosphorus and no bone symptoms.

STATISTICAL ANALYSIS

Continuous data were tested for normal distribution with the Kolmogorov -Smirnov test. Parametric distributions are presented by mean and Standard Deviation (SD). Non-parametric data are expressed in median and interquartile range (Q1-Q3).

The Spearman test was used to test correlation. Fisher exact test or Chi-square test were employed, when appropriate. The median preoperative PTH was calculated and used in contingency tables to separate two groups: PTH above the median or PTH equal of under the median.

RESULTS

During the period of the study, 53 patients with 2HPT were operated on. The analysis was possible in 51 cases (Table 1). Before the operation PTH varied from 425 to 6,964 pg/mL. Follow-up of up to 72 months. There were seven deaths in this period.

TABLE 1 PREOPERATIVE DATA OF THE PATIENTS

Gender (number of patients)	male (27)	female (24)
Mean age (range)	46 years (9-71)	
Time of dialysis	9 years (Q1-Q3; 9-12)	
Median PTH	2,103 pg/mL (Q1-Q3;1,554-3,105)	
Median calcium	10.3 mg/dL (Q1-Q3; 9.7-10.3)	
Mean phosphorus	5.4 mg/dL (SD 1.3)	

PTH: parathyroid hormone.

Postoperative PTH values ranged from zero to 1215 pg/mL (median zero and Q1-Q3 0-75 pg/mL). PTH after parathyroidectomy was undetectable in 28 cases (54.9%). In eight patients (15.7%), the PTH was lower than 16 pg/mL, and in 10 (19.6%) the PTH values were between 16 and 87 pg/mL. Early postoperative PTH was higher than 87 pg/mL in five cases (9.8%).

The influence of preoperative PTH in postoperative levels was remarkable. Table 2 shows that most patients with preoperative values above the median

had a detectable postoperative PTH. Conversely, when preoperative PTH was below the median most patients had undetectable levels postoperatively.

TABLE 2 DETECTABLE OR UNDETECTABLE POSTOPERATIVE PTH ACCORDING TO THE MEDIAN OF PREOPERATIVE PTH

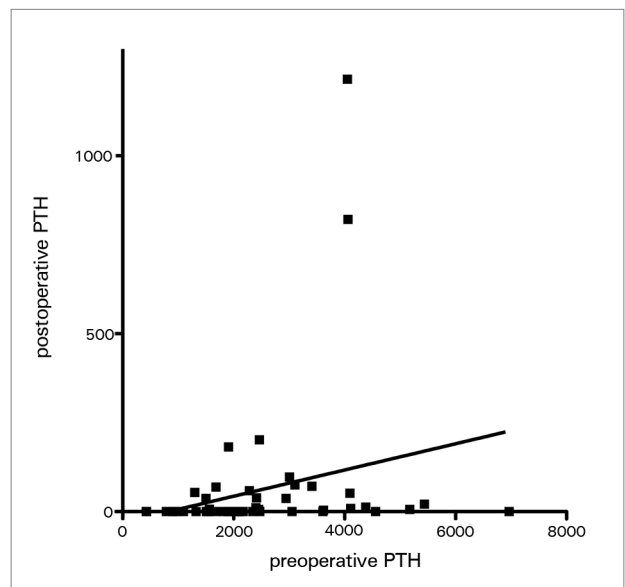
	Postoperative PTH	
	PTH = 0	PTH > 0
Preoperative PTH ≤ median	21	5
Preoperative PTH > median	7	18

p: 0,0002, Fisher Exact Test; PTH: parathyroid hormone.

When the postoperative PTH value was below the upper normal limit of the method (87pg/mL) no persistent disease occurred. However, the absolute may not be considered a good indicator of persistence, because one of the five patients with postoperative PTH above 87pg/mL did not have persistent disease.

There was a significant correlation of preoperative PTH and postoperative PTH with Spearman R coefficient of 0.43 (p = 0.002), as shown in Figure 1.

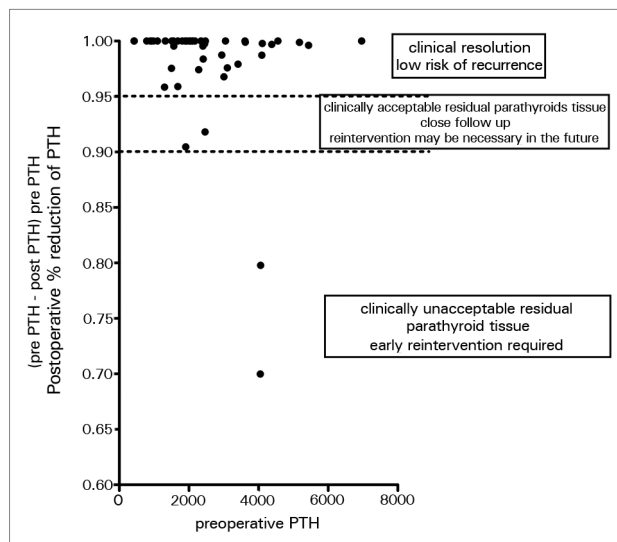
Figure 1. Correlation of preoperative and early postoperative PTH. PTH: parathyroid hormone.



A relative decay of PTH was apparently a better indicator of persistent disease. The relative reduction of PTH varied from 1 to 0.7 (100% to 70%). Figure 2 shows the distribution of PTH reduction according to preoperative PTH and clinical outcome.

All cases with more than 95% decrease of PTH had long-term resolution of the 2HPT. In two cases

Figure 2. Relative early decrease of PTH and clinical outcome (Dot-plot). PTH: parathyroid hormone.



with decrease between 90% and 95%, the follow up suggested a supernumerary parathyroid gland, but metabolic goals were adequate and no further operation was necessary. Less than 80% decrease was associated with persistent disease, with unsatisfactory metabolic results and another intervention was advised.

Clinically significant persistence occurred in two cases, with early values of 821 (79.8% decrease) and 1215 pg/mL (70% decrease). Four and five glands were excised, respectively. In these cases bone symptoms, calcium and phosphorus levels presented non significant alteration. Both patients abandoned the follow up, and 2HPT clearly persisted. Even though, the clinical course in the long run is unknown, the outcome persistence was established.

In two other cases, postoperative levels of PTH were very suggestive of persistent parathyroid tissue. Their postoperative PTHs were 182 (90.5% decrease) and 202 pg/mL (91.8% decrease). However in both cases symptoms and mineral metabolism improvement occurred and no early intervention was required. In the second case, a reintervention was only necessary after six years.

DISCUSSION

The present study shows that in severe advanced 2HPT a very high preoperative PTH levels is frequently related to some detectable PTH during the first days after the parathyroidectomy, in regular dialysis patients.

Of the 1156 patients submitted to total parathyroidectomy with forearm autograft in study in Japan, 49 (4.2%) patients had persistent disease. In that study, persistent 2HPT was defined if the lowest postoperative PTH concentration measured on 1st or 2nd day was higher than 60pg/mL (upper normal limit of used method).⁵ According to that cut level, we would have 9.8% of persistent cases in the present study, but we had only two (3.8%) patients with early unacceptable outcome. In this view, using absolute postoperative PTH may be confusing. So, it is possible to have negative cases for persistence in patients with PTH concentrations higher than upper normal limit of the method used. In our view, a relative decay is better indicator of successful operation or persistence.

However, low or undetectable postoperative PTH virtually rule out persistent disease. Similarly to the literature,⁵ no one patient who had postoperative PTH concentration lower than upper limit normal had persistent disease. So, it is more difficult to have persistent 2HPT in patients with PTH concentrations lower than upper normal limit.

It seems reasonable to consider that very high postoperative PTH levels clearly point to a hyperplastic residual or supernumerary gland. However, the absolute value of PTH should be interpreted with caution, as results as high as the upper reference to the method may not reflect a problematic residual gland with unacceptable outcome. Indeed, the relative decrease seems more reliable.

We suggest that the relative decrease of PTH in the early days after the operation is more informative. Although a very high preoperative PTH value may preclude the observation of undetectable postoperative PTH, a reduction of more than 95% indicates a successful operation. Conversely, if postoperative reduction is less than 80%, it may indicate persistent disease requiring aggressive surgical or medical therapy.

In sporadic primary HPT, intraoperative PTH is very helpful in guiding the surgeon to continue the operation if unsatisfactory decrease of PTH occurs.¹³ In multiglandular primary hyperplasia, the use of PTH during the operation has a more limited value and more severe criteria are apparently more useful.¹⁴

In 2HPT the interpretation of intraoperative PTH is also difficult and there are different suggestions to its use.^{15,16} The impact of 7-84 fragments in intraoperative PTH is significant, and there may be a significant window of uncertainty during

the operation in dialysis patients. Thus, although intraoperative PTH is valid in 2HPT, the results are not so straightforward as in sporadic primary HPT to clearly predict a successful operation, especially in subtotal parathyroidectomy.

Patients under dialysis with 2HPT require multidisciplinary care. In general, the surgeon has contact with the patient during a short period of time before and after the operation. For practical reasons, most of the long-term follow up is under the supervision of the nephrologist. If both surgeons and clinicians are aware of a possible residual hyperplastic or supernumerary parathyroid gland, the decision to repeat imaging scans and to perform a reoperation may be made without long delay. The problem of postponing the diagnosis is the misleading attribution of the recurrence to a subtotal stump hyperplastic growth or the confounding secretion of a hyperfunctioning parathyroid autograft.

If an insufficient decrease of PTH is observed until the third postoperative day, despite hypocalcemia, the surgeon can be alerted of a relevant supernumerary or residual gland. Depending on the facility, a localizing study may be quickly performed and a reoperation conducted before fibrosis and the postsurgical inflammation are risky. Early reintervention is usually recommended before the first week of the initial operation, as the healing process that ensues thereafter normally causes a very difficult dissection.

As we observed, patients with very high preoperative PTH probably may had circulating 7-84 fragments the day after the operation. Theoretically, the 2nd or the 3rd day after the operation would be the best periods to sample PTH. In this period 7-84 fragments are lower and the autograft secretion is expected to be very low. To postpone the evaluation of postoperative PTH more than one week would impact in the practical objective, as the reoperation would also require to be delayed due to the healing process and the risks.

CONCLUSIONS

PTH levels during the first week after a total parathyroidectomy with autograft are correlated to preoperative levels and not all patients will have undetectable PTH.

The relative decrease will be very useful, and a decrease of 95% or more indicates a successful operation. Conversely, a decrease less than 80% suggests persistent disease and early reintervention required.

REFERENCES

- Santos RO, Ohe MN, Carvalho AB, Neves MC, Kunii I, Lazaretti-Castro M, et al. Total parathyroidectomy with presternal intramuscular autotransplantation in renal patients: a prospective study of 66 patients. *J Osteoporos* 2012;2012:631243. DOI: <http://dx.doi.org/10.1155/2012/631243>
- Conti-Freitas LC, Foss-Freitas MC, Lucca LJ, da Costa JA, Mamede RC, Foss MC. Dynamics of parathyroid hormone secretion after total parathyroidectomy and autotransplantation. *World J Surg* 2009;33:1403-7. PMID: 19404704 DOI: <http://dx.doi.org/10.1007/s00268-009-0057-8>
- Magnabosco FF, Tavares MR, Montenegro FL. Surgical treatment of secondary hyperparathyroidism: a systematic review of the literature. *Arq Bras Endocrinol Metabol* 2014;58:562-71. PMID: 25166048 DOI: <http://dx.doi.org/10.1590/0004-2730000003372>
- Goldenstein PT, Elias RM, Pires de Freitas do Carmo L, Coelho FO, Magalhães LP, Antunes GL, et al. Parathyroidectomy improves survival in patients with severe hyperparathyroidism: a comparative study. *PLoS One* 2013;8:e68870. DOI: <http://dx.doi.org/10.1371/journal.pone.0068870>
- Tominaga Y, Katayama A, Sato T, Matsuoka S, Goto N, Haba T, et al. Re-operation is frequently required when parathyroid glands remain after initial parathyroidectomy for advanced secondary hyperparathyroidism in uraemic patients. *Nephrol Dial Transplant* 2003;18:iii65-70. DOI: <http://dx.doi.org/10.1093/ndt/gfg1017>
- Tominaga Y, Numano M, Tanaka Y, Uchida K, Takagi H. Surgical treatment of renal hyperparathyroidism. *Semin Surg Oncol* 1997;13:87-96. PMID: 9088064 DOI: [http://dx.doi.org/10.1002/\(SICI\)1098-2388\(199703/04\)13:2<87::AID-SSU4>3.0.CO;2-Y](http://dx.doi.org/10.1002/(SICI)1098-2388(199703/04)13:2<87::AID-SSU4>3.0.CO;2-Y)
- Arap SS, Cordeiro AC, Brandão LG, Ferraz AR, Michaluart Jr P, et al. Secondary hyperparathyroidism: prognostic factors of graft-dependent recurrence after total parathyroidectomy and parathyroid autotransplantation. *Rev Bras Cir Cabeça Pescoço* 2010;39:24-32.
- d'Alessandro AF, Montenegro FL, Brandão LG, Lourenço Jr DM, Toledo Sde A, Cordeiro AC. Supernumerary parathyroid glands in hyperparathyroidism associated with multiple endocrine neoplasia type 1. *Rev Assoc Med Bras* 2012;58:323-7. DOI: <http://dx.doi.org/10.1590/S0104-42302012000300012>
- Donckier V, Decoster-Gervy C, Kinnaert P. Long-term results after surgical treatment of renal hyperparathyroidism when fewer than four glands are identified at operation. *J Am Coll Surg* 1997;184:70-4. PMID: 8989303
- de Menezes Montenegro FL, Custódio MR, Arap SS, Reis LM, Sonohara S, Castro IV, et al. Successful implant of long-term cryopreserved parathyroid glands after total parathyroidectomy. *Head Neck* 2007;29:296-300. DOI: <http://dx.doi.org/10.1002/hed.20506>
- Ohe MN, Santos RO, Hojaj F, Neves MC, Kunii IS, Orlandi D, et al. Parathyroid carcinoma and hungry bone syndrome. *Arq Bras Endocrinol Metabol* 2013;57:79-86. DOI: <http://dx.doi.org/10.1590/S0004-27302013000100011>
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease- Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009;(113):S1-130.
- Udelsman R, Donovan P, Shaw C. Cure predictability during parathyroidectomy. *World J Surg* 2014;38:525-33. PMID: 24240672 DOI: <http://dx.doi.org/10.1007/s00268-013-2327-8>
- Nilubol N, Weisbrod AB, Weinstein LS, Simonds WF, Jensen RT, Phan GQ, et al. Utility of intraoperative parathyroid hormone monitoring in patients with multiple endocrine neoplasia type 1-associated primary hyperparathyroidism undergoing initial parathyroidectomy. *World J Surg* 2013;37:1966-72. DOI: <http://dx.doi.org/10.1007/s00268-013-2054-1>

15. Bieglmayer C, Kaczirek K, Prager G, Niederle B. Parathyroid hormone monitoring during total parathyroidectomy for renal hyperparathyroidism: pilot study of the impact of renal function and assay specificity. *Clin Chem* 2006;52:1112-9. DOI: <http://dx.doi.org/10.1373/clinchem.2005.065490>
16. Ohe MN, Santos RO, Kunii IS, Carvalho AB, Abrahão M, Neves MC, et al. Intraoperative PTH cutoff definition to predict successful parathyroidectomy in secondary and tertiary hyperparathyroidism. *Braz J Otorhinolaryngol* 2013;79:494-9. PMID: 23929152 DOI: <http://dx.doi.org/10.5935/1808-8694.20130088>