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Original Communications

Parathyroidectomy in patients with chronic kidney disease: Impacts of different techniques on the biochemical and clinical evolution of secondary hyperparathyroidism

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ABSTRACT

Background. Parathyroidectomy (PTx) decreases the mortality rate of refractory secondary hyperparathyroidism (rSHP) due to chronic kidney disease. A consensus regarding which techniques of PTx are associated with better outcomes is not available. The aims of this study are to evaluate the clinical and laboratory evolution of 49 hemodialysis patients with rSHP who underwent PTx using different techniques.
Methods. Patients underwent subtotal PTx (sub-PTx) or total PTx with autotransplantation (AT) of 45 (PTx-AT_{45}) or 90 parathyroid fragments (PTx-AT_{90}) and were followed for 12 months. We analyzed the expression of proliferating cell nuclear antigen (PCNA), calcium-sensing receptor (CasR), vitamin D receptor (VDR), fibroblast growth factor receptor-1 (FGFR1), sodium-dependent phosphate cotransporter-1 (PIT1), and Klotho in parathyroid glands.
Results. Baseline median serum intact parathyroid hormone (iPTH) levels were 1,466 (1,087–2,125) pg/mL; vascular calcification scores correlated with serum iPTH ($r = 0.529$; $P = .002$) and serum phosphate levels ($r = 0.389$; $P = .028$); and Klotho expression was negatively correlated with serum phosphate levels ($r = –0.4$; $P = .01$). After 12 months, serum iPTH and alkaline phosphatase levels were significantly controlled in all groups, as was bone pain. The proportions of patients with serum iPTH levels within the ranges recommended by Kidney Disease: Improving Global Outcomes were similar among the treatment groups. During the hungry bone disease (HBS), patients received 3,786 g (1,412–7,580) of elemental calcium, and a trend toward a positive correlation between the cumulative calcium load at the end of follow up and VC score post-PTx was noted ($r = 0.390$; $P = .06$). Two cases evolved to clinically uncontrolled hyperparathyroidism in the sub-PTx group. The expression patterns of PCNA, VDR, CasR, PIT1, FGFR1, and Klotho in parathyroid glands did not correlate with serum systemic iPTH levels or the duration of HBS.
Conclusions. All 3 operative techniques were effective at controlling rSHP, both in clinical and laboratory terms. Neither the quantity nor quality of parathyroid fragments influenced serum systemic iPTH and AT-iPTH levels. The cumulative calcium load appeared to correlate with the VC score and may have affected its progression. The effects of phosphate restriction on Klotho expression in human parathyroid glands and the subsequent decrease in FGF23 resistance must be addressed in further studies.

Over the past decade, a marked improvement has occurred in the clinical treatment of secondary hyperparathyroidism (SHP) due to chronic kidney disease (CKD), which has been achieved through the introduction of vitamin D receptor activators, phosphate binders, and cinacalcet hydrochloride, as well via improvements in dialysis

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treatment.[1,2] These achievements have led to better control of SHP, followed by a substantial decrease in the need for parathyroidectomy (PTx) in different parts of the world.[3,4]

However, PTx remains a useful therapeutic treatment for patients with clinically refractory SHP (rSHP).[5,6] In Brazil, approximately 11% of dialysis patients were estimated to have rSHP in 2011, corresponding to approximately 9,000 patients receiving chronic dialysis treatment.[7] This scenario may be similar in many countries in which full clinical treatments are not widely available. Notably, PTx is effective for rSHP, improves survival, and is less expensive than the long-term use of treatment with cinacalcet hydrochloride.[6,8-10]

The choice of technique for the PTx (i.e., subtotal PTx [sub-PTx], total PTx, or total PTx with autotransplantation [PTx-AT]) has relied on the surgeon's preference and abilities[11,12]; however, the clinical effects of different techniques of PTx are a matter of debate, as the proportion of patients who undergo PTx and develop persistent hypo- or hyperparathyroidism is not negligible.[13-16] In contrast, several authors recommend PTx-AT as the method of choice in the operative treatment of SHP, arguing that a reoperation at the site of AT in the forearm is simpler than a reoperation in the neck for patients with recurrent disease.[17] In contrast, the parathyroid tissue used in the AT cannot produce a sufficient amount of intact parathyroid hormone (iPTH), whereas the parathyroid tissue remaining in the neck is more likely to provide adequate levels of this hormone. Another currently unanswered question is which technique is associated with less cumulative calcium (Ca) load experienced during hungry bone syndrome (HBS).

Definitions of appropriate post-PTx serum systemic parathyroid hormone (PTH) levels are even more complicated.[18] Currently, the use of the same levels recommended by different guidelines for patients with stage 5D of CKD are accepted in clinical practice. The National Kidney Foundation, through Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, has recommended serum PTH levels of 150 to 300 pg/mL, whereas guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) suggest that PTH levels should remain between 2 to 9 times the normal upper limit for the assay method. The target level of PTH proposed by the Japanese Society for Dialysis Therapy (JSDT) ranges from 60 to 180 pg/mL.[19-21]

To the best of our knowledge, the hypothesis that the amount of parathyroid tissue used in PTx-AT (the number of fragments) or left in the neck (sub-PTx) exerts different effects on long-term, serum systemic PTH levels and clinical outcomes has not been tested formally. Similarly, the relation between the abnormalities in the parathyroid tissue and the clinical evolution or AT function has not yet been described completely. Previous studies have focused primarily on comparing clinical aspects of different techniques or have proposed meta-analyses of heterogeneous studies.[17,22]

The objectives of the present study were to evaluate clinical and laboratory outcomes in a cohort of 49 patients undergoing hemodialysis (HD) with rSHP who underwent PTx-AT using 45 or 90 parathyroid fragments or sub-PTx. The influence of the abnormalities of the parathyroid tissue on the clinical evolution and biochemical parameters were assessed by analyzing the expression of proliferating cell nuclear antigen (PCNA), calcium-sensing receptor (CasR), vitamin D receptor (VDR), fibroblast growth factor receptor-1 (FGFR1), sodium-dependent phosphate cotransporter-1 (PIT1), and Klotho in the parathyroid gland. These markers were chosen based on the pathophysiology of SHP. PCNA is related to the degree of monoclonal proliferation of parathyroid cells and may have an effect on recurrence rates of sHPT. The expression of CasR and VDR may signal both the severity of pathologic changes in the parathyroid tissue and its ability to respond to therapeutic interventions, such as calcimimetics or active vitamin D. An indirect estimate of responsiveness to phosphate and resistance to FGF23 was performed by analyzing the expression levels of FGFR1, PIT1, and Klotho in the parathyroid gland.

Materials and Methods

Study design

This study was performed in patients with CKD complicated with rSHP who were undergoing HD. From January 2012 to July 2013, 49 adult patients who attended the CKD-mineral and bone disorder (MBD) outpatient clinic in the *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* (HC-FMUSP) underwent one of the following operative procedures: total PTx with AT of 45 parathyroid fragments (PTx-AT_{45}), total PTx with AT of 90 parathyroid fragments (PTx-AT_{90}), and sub-PTx. Patients were chosen sequentially according to the time frame of the study. The minimum follow-up period was 12 months.

Selection criteria included clinically stable patients with stage 5 CKD on HD for at least 3 months; a diagnosis of clinically refractory SHP expressed as persistent serum iPTH levels >800 pg/mL, associated with or without hypercalcemia/hyperphosphatemia, soft tissue calcification, or disabling bone disease, or the presence of voluminous parathyroid glands on ultrasonography (>1 cm^3). Exclusion criteria included severe intercurrences in the postoperative period (i.e., prolonged hypotension, septic, or hemorrhagic shock); wound infection at the neck or at the site of the AT implant; loss of follow-up due to kidney transplantation, new AT surgery with cryopreserved parathyroid fragments, or persistence of SHP due to an ectopic or supernumerary parathyroid gland.

This study was approved by the Ethical and Research Committee of HC-FMUSP under numbers/CAEE 0882/2011 and 00828412.8.0000.0068. Informed consent was obtained from all patients, and the study was performed in accordance with the precepts of the Declaration of Helsinki.

Definitions and outcomes

The duration of HBS was defined as the period immediately after PTx until serum alkaline phosphatase (AP) levels reached the reference range or remained stable on 2 separate occasions 6 months after PTx, or as defined by the attending nephrologist in the absence of the previous 2 conditions.

Calcium (Ca) and calcitriol cumulative loads were calculated beginning on the first day post-PTx until the end of HBS or at the 12-month follow-up visit. Bone pain was defined as an unpleasant deep and intense, sensorial experience localized in a majority of the skeleton that led to analgesic use on most days of a week. Pathologic fracture was defined as a fracture that would not otherwise occur in the absence of pathologic weakening of the bone due to CKD-MBD.

We defined 3 categories based on the KDIGO recommendations for serum systemic iPTH levels to classify the evolution of HBS 12 months after PTx[19]: "inside the target," which included patients with serum iPTH levels between 2 and 9 times the upper limit of the reference range (130–585 pg/mL); "lower than target" patients had serum iPTH levels <2 times the lower limit of the range (<130 pg/mL); and "higher than target," which included patients with serum iPTH levels >9 times the upper limit of the range (>585 pg/mL).

Operative procedures

PTx was performed according to a modification of the Wells technique,[14,23] which consists of total removal of parathyroid glands followed by immediate AT of parathyroid fragments (~2 mm^2 each) into 1 or 2 pockets under the fascia of the brachioradialis muscle in the forearm without vascular access. Sub-PTx consisted of the resection of parathyroid tissue, leaving behind tissue fragments approximately equivalent to the size of 2 normal glands in the stump. The stump was marked with a nonabsorbable suture should the need for operative revision become necessary.

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