

Clinical Study

Total Parathyroidectomy with Presternal Intramuscular Autotransplantation in Renal Patients: A Prospective Study of 66 Patients

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Surgical treatment of secondary (SHPT) and tertiary hyperparathyroidism (THPT) may involve various surgical approaches. The aim of this paper was to evaluate presteral intramuscular autotransplantation of parathyroid tissue as a surgical option in SHPT and THPT treatment. 66 patients with renal chronic disease underwent surgery from April 2000 to April 2005 at Universidade Federal São Paulo, Brazil. There were 38 SHPT patients (24 women/14 men), mean age of 39 yrs (range: 14–58), and 28 THPT patients (14 women/14 men), mean age of 43.4 yrs (range: 24–62). Postoperative average followup was 42.9 months (range: 12–96). Postoperative intact PTH increased throughout followup from 73.5 pg/mL to 133 pg/mL on average from 1st to the 5th year, respectively, in SHPT and from 54.9 pg/mL to 94.7 pg/mL on average from 1st to 5th year, respectively, in THPT group. Definitive hypoparathyroidism was observed in 4 (6.06%) patients and graft-dependent recurrence in 6 (9.09%). Presternal intramuscular autotransplantation of parathyroid tissue is a feasible and safe surgical option in SHPT and THPT treatment.

1. Introduction

Secondary hyperparathyroidism is a frequent and potentially severe complication in patients with renal chronic disease, evolving metabolic bone disease, severe atherosclerosis, and undesirable cardiovascular events. Despite recent advances in medical therapy, surgical approach is necessary in a considerable number of uremic patients [1]. The best surgical approach for renal hyperparathyroidism is yet to be defined. Controversy remains thus raising relevant questions regarding treatment election, once neither high postsurgical recurrence rates nor risks of definitive hypoparathyroidism are intended.

The aim of this paper was to evaluate hyperparathyroidism recurrence rates and prevalence of definitive hypoparathyroidism in a long-term followup after total parathyroidectomy with presteral intramuscular autotransplantation in patients with secondary and tertiary hyperparathyroidism.

2. Patients and Methods

2.1. Study Design. This is a prospective study on a cohort of operated patients treated at a university referral center. All surgeries were performed by the same surgeon.

This investigation was approved by the UNIFESP/EPM Ethics Committee (approval no. CEP 1091/05).

2.2. Patients. Two hundred and twelve patients underwent parathyroidectomy from April 2000 to April 2005 at Hospital São Paulo and Hospital do Rim UNIFESP/EPM, São Paulo, Brazil. Those patients were followed at the Renal Osteodystrophy Unit in our institution and were referred to surgical treatment in face of persistent hypercalcemia not responsive to medical interventions and/or persistent hyperphosphatemia despite the continued use of dietary phosphorus restriction and phosphate-binding agents, symptoms as intractable pruritus, severe bone pain, fractures or high risk of fracture, skeletal deformities, extra

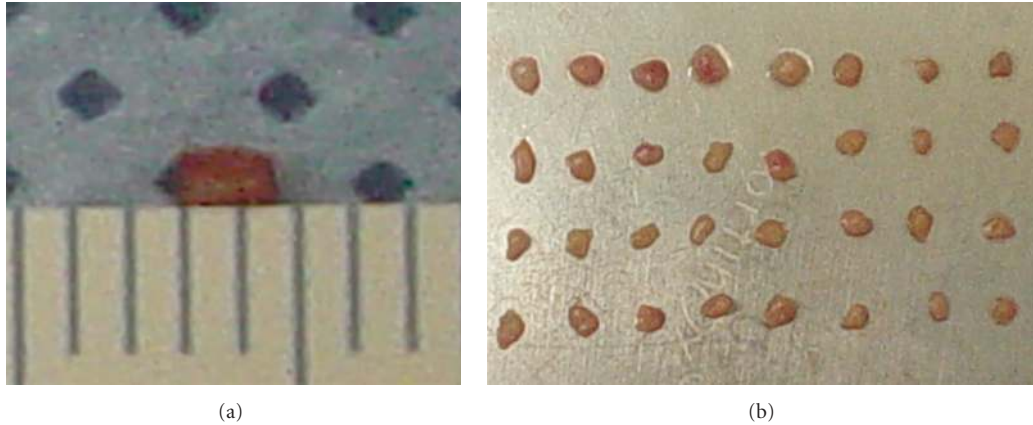


FIGURE 1: Parathyroid gland fragments sized 2 mm^3 selected for presternal autotransplantation.

TABLE 1: Characteristics of patients and preoperative laboratory findings.

	SHPT	THPT
N (number of patients)	38	28
Sex (female : male)	24 : 14	14 : 14
Mean age (years)	39.2 (14–58)	43.4 (24–62)
Years on dialysis	7.8 (1–13)	6.12 (2–20)
Years of renal graft		2.6 (1–7)
iCa	1.35 (1.18–1.40)	1.59 (1.42–1.77)
P	6.6 (4.5–11.8)	2.7 (1.6–6.3)
AP	877 (130–2900)	311 (74–1304)
iPTH	1711 (516–2500)	442 (109–1758)

SHPT: secondary hyperparathyroidism; THPT: tertiary hyperparathyroidism, iCa: Serum-ionized calcium, P: phosphorus; AP: alkaline phosphatase; iPTH: intact parathyroid hormone. Reference values: iCa: 1.11–1.40 mmol/L; P: 2.3–4.6 mg/dL; AP: 35–129U/L; iPTH: 10–65 pg/mL.

skeletal calcifications, development of calciphylaxis, and radiographic evidence of renal osteodystrophy. From the 212 patients who underwent total parathyroidectomy with presternal autotransplantation, 66 had at least 1 year of postoperative followup with enough reported data to be eligible for the study.

These 66 patients were divided into two groups: the first included renal patients in dialysis treatment ($N = 38$), defined as secondary hyperparathyroidism (SHPT) group and the second group included patients with kidney graft ($N = 28$), defined as tertiary hyperparathyroidism (THPT) group. Secondary hyperparathyroidism is characterized as an acquired disorder seen in end-stage renal disease, in which the uremic state presents a continuous stimulus to the parathyroid glands. We included in the SHPT group patients under dialysis treatment who presented severe hyperparathyroidism without hypercalcemia. Tertiary hyperparathyroidism group was composed by renal patients with kidney transplant with nonsuppressible parathyroid hyperplasia, with persistent increased iPTH levels and hypercalcemia even after restoration of normal renal function.

Hypercalcemia after kidney transplantation is usually due to hyperparathyroidism that persists from the preceding chronic kidney disease period [2].

Serum-ionized calcium (iCa), phosphorus (P), alkaline phosphatase (AP), and intact parathyroid hormone (PTH) were measured before parathyroidectomy (Table 1) and yearly after surgery in all patients from both groups.

Definitive hypoparathyroidism was described when PTH measurements under 10 pg/mL endures 1 year after parathyroidectomy, with normal or low-serum calcium levels under vitamin D and oral calcium replacement.

Hyperparathyroidism recurrence after surgery was defined when high levels of intact PTH were observed throughout late postoperative followup that failed to respond to medical/pharmacological management.

2.3. Methods. Total parathyroidectomy with intramuscular presternal autotransplantation was performed in 66 patients from April 2000 to April 2005. Those patients were evaluated in a prospective manner 1 to 8 years after surgery. All of them had at least four-gland excision confirmed by frozen section examination and/or intraoperative PTH measurement (IO-PTH available in 43 patients) so as to confirm surgical cure.

Removed parathyroid glands were carefully examined in order to select a parathyroid area (non nodular region) for implant and cryopreservation. The selected parathyroid fragment was gently diced into small pieces measuring approximately 2.0 mm^3 , and 60 to 65 pieces of suitable parathyroid graft were obtained by this technique (Figure 1). Around 30 parathyroid fragments were implanted in presternal musculature over a single area of 1.5 cm in length.

A horizontal 1.5 cm incision was made over the upper one-third of the sternum above left 2nd intercostal space (Figure 2). Pectoralis major muscle insertion at sternum bone [3–5] was identified followed by fascia and muscle fibers dissection in an attempt to perform a 1.5 cm graft pocket where parathyroid fragments were implanted. This grafted area had sternum bone as posterior boundary.

Muscular fascia and the superficial part of the presternal musculature are sutured with a nonabsorbible filament.



FIGURE 2: Intramuscular presternal grafted area: final aspect.

The suture prevented parathyroid graft extrusion and contributed as a marker of the grafted area.

After skin incision had been closed, remaining sterile parathyroid pieces were frozen at -70°C in a solution containing 60% of RPMI or DMEM, 30% of fetal bovine serum and 30% of DMSO (dimethylsulfoxide), thus cryopreserved for further reimplant, if needed.

Intraoperative PTH (IO-PTH) was performed in an attempt to confirm total removal of the parathyroid glands, so as to avoid overlooking remaining or supernumerary hyperfunctioning glands. IO-PTH was measured by resorting to the Elecsys PTH Immunoassay (Elecsys 1010 System, Roche, Mannheim, Germany). The time required to carry out the assay is 9 minutes, and reference values are 10–70 pg/mL. Peripheral venous blood sample (4.0 mL) was obtained immediately after induction of anesthesia and 20 minutes after removal of all parathyroid glands [6, 7].

Phosphorus, total alkaline phosphatase, and creatinine were measured by means of standard automatic assays (Hitachi 912, Roche). Serum-ionized calcium was measured by using an ion-specific electrode (AVL 9180 Electrolyte Analyzer, Roswell, GA, USA). Parathyroid hormone was measured by immunometric assay (Immulite, DPC, Med-Lab) (Table 1).

3. Results

Overall, 66 patients underwent total parathyroidectomy with presternal intramuscular autotransplantation and were evaluated in a prospective manner in an average followup of 42.9 months (ranging from 12 to 96 months). There were 38 patients in SHPT group, of whom 24 were women and 14 were men, with a mean age of 39.2 years (ranging from 14 to 58). There were 28 patients in THPT group, 14 female and 14 male, aged 43.4 years on average, ranging from 24 to 62. Patients from SHPT group presented with an average of 7.8 years under dialysis treatment before parathyroidectomy, and THPT group comprised patients who had undergone dialysis treatment for an average of 6.12

years before receiving a kidney graft, with an average of 2.6 years of functional renal graft before parathyroidectomy (Table 1).

Intraoperative PTH measurements revealed a percentage decrease of 87% on average in patients considered cured, ranging from 67.8% to 94.4%. Only one patient was not cured after four-gland excision, whose intraoperative PTH decrease was only 62.1%. Moreover, further surgical exploration revealed a 5th parathyroid gland, which was excised followed by 70.2% intraoperative PTH level decrement.

Postoperative PTH levels increased throughout follow-up in both groups, from 73.5 pg/mL on average in the first year to 133 pg/mL on average in the 5th in SHPT group and from 54.9 pg/mL on average in the first year to 94.7 pg/mL on average in the 5th in THPT (Table 2).

Definitive hypoparathyroidism was observed in 4 (6.06%) patients, 3 of whom in SHPT group and 1 in THPT group.

Graft-dependent recurrence was observed in 6 patients (Table 3, bold data). All of them occurred in patients under dialysis treatment years after total parathyroidectomy with presternal autotransplantation. Diagnosis of graft-dependent recurrence was confirmed by positive sestamibi ^{99m}Tc investigation, followed by presternal graft surgical removal.

Bone biopsy with mineralized bone histology after double tetracycline labeling was performed in 11 patients (16.6%) prior to surgery. The results observed were osteitis fibrosa in 6 patients (with osteoporosis components in 2 and aluminum staining in 3), mixed uremic osteodystrophy in 4 (with osteoporosis components in 2, aluminum staining in 1), and adynamic bone in 1 patient.

4. Discussion

Secondary hyperparathyroidism is a common complication in patients with renal chronic disease. Before currently available medical and surgical therapies, SHPT used to result in considerable morbidity and mortality, including crippling bone disease [2]. It is worth highlighting that the ideal treatment for patients with renal chronic disease concerns kidney graft. Nevertheless, not all patients are eligible for this treatment, once due to clinical counter-indications, or unfavorable socioeconomic-educational limitations. Unfortunately, we still have difficulties in providing kidney transplantation for all patients with renal chronic failure in our country, thus exposing them to an undesirable long-term dialysis treatment.

The longer survival of renal chronic disease patients increased the incidence of symptomatic hyperparathyroidism condition [8]. The incidence of parathyroidectomy in renal patients is about 5 per 1,000 patients-year during the first 2 to 3 years of dialysis; however, the rates rise to over 40 per 1,000 patients-year among patients who underwent maintenance dialysis for 10 years or more [9]. Similarly, the prevalence of parathyroidectomy in end-stage renal disease ranges from 9.2% after 10–15 years in dialysis to 20.8% after 16–20 years in dialysis treatment

TABLE 2: Intact PTH (pg/mL) measurements in the followup.

	1st year	2nd year	3rd year	4th year	5th year	>5 yrs
SHPT (<i>n</i> = 38)	73.5	82	80	82	133	102.6
THPT (<i>n</i> = 28)	54.9	61.7	70.5	74.3	94.7	98.5

SHPT: secondary hyperparathyroidism group; THPT: tertiary hyperparathyroidism group; reference value for iPTH: 10–65 pg/mL.

TABLE 3: Patients followup with graft-dependent recurrence years after surgery.

Recurrence	1st-year PTH/Cai	2nd-year PTH/Cai	3rd-year PTH/Cai	4th-year PTH/Cai	5th-year PTH/Cai	After 5 yrs PTH/Cai
Patient 1	937/0.9					
Patient 2	13/1.40	51/1.4	1165/1.29			
Patient 3	66/1.16	84/1.27	198/1.3		611/1.3	
Patient 4	67/1.16	104/1.29	132/1.08		162/1.28	1155/1.02
Patient 5	22/0.90		168/1.56	569/1.53		
Patient 6					925/1.3	

Reference values: iCa: 1.11–1.40 mmol/L; iPTH: 10–65 pg/mL.

[1]. Therefore, parathyroidectomy rates rise along with time on dialysis treatment [9, 10]. In patients eligible for surgery, parathyroidectomy is generally considered when hyperparathyroidism is severe and refractory to medical management, usually after a therapeutic trial of calcitriol and a vitamin D analog, or when medical management to reduce iPTH levels results in unacceptable rises in levels of serum calcium and/or phosphorus, or when medical management is not tolerated because of adverse effects [2]. Our study reviewed a patient cohort prior to the use of calcimimetics, which may play an effective role in the clinical management of renal patients; however, such drug is still not available in our country for all chronic renal disease patients. Even in kidney-transplanted patients, parathyroidectomy is an important therapeutic approach, appearing to be safe for renal function regardless of the technique employed [11].

The best surgical approach for renal hyperparathyroidism remains controversial in the literature. In 1960, Stanbury et al. were the first to perform a successful parathyroidectomy with a subtotal technique, where a parathyroid fragment remained in the neck, supplied by its own blood vascular source [12]. In an attempt to avoid high postoperative hyperparathyroidism recurrence, in 1967 Ogg proposed total parathyroidectomy for renal patients with no kidney transplant perspective [13]. This technique relies on the idea that microscopic residual parathyroid tissue is present in the thymus [14], which should be able to sustain an adequate hormone level and thus prevent the adynamic bone disease [15]. Nonetheless, definitive hypoparathyroidism is a harmful condition, mainly in kidney transplant patients in whom hypoparathyroid states are highly symptomatic and difficult to control. Moreover, total parathyroidectomy not followed by immediate parathyroid tissue reimplantation may not be indicated for patients with renal chronic disease awaiting kidney transplantation [2]. Once this technique with total parathyroidectomy without autotransplantation leads to harmful definitive hypoparathyroidism condition, Wells et al., in 1975 and 1977, reported their experience in total

parathyroidectomy with parathyroid autotransplantation in forearm musculature and parathyroid tissue cryopreservation for further reimplant if needed [16–18]. This innovative approach has enabled into a new surgical view: parathyroid transplantation, cryopreserved parathyroid tissue viability, and cryopreserved parathyroid transplantation. Therefore, total parathyroidectomy with forearm autograft, as proposed by Wells et al. in 1975, has been considered the standard procedure ever since [16]. In this technique, parathyroid fragments are grafted into forearm brachioradialis or flexor muscle group, where each parathyroid fragment is placed in a separate bed. This approach is in agreement with the idea of feasible recognition and treatment of possible graft-dependent recurrence. Parathyroid graft would be easily recognized in this location, and excision might be performed under local anesthesia. In addition, parathyroid graft function would then be evaluated based on comparative PTH measurements between grafted and nongrafted arm.

Nevertheless, that technique has presented some restrictions. In 1978, Wells described four (13%) normocalcemic patients with no oral medicine intake, in whom PTH measurements were undetectable in grafted arm [19]. Regarding the graft removal experience, in 1979 Wells reported three (7.5%) patients with graft-dependent hyperparathyroidism, of whom one presented with persistent hyperparathyroidism even after parathyroid graft was excised [20]. Seeking to avoid these undesirable recurrence outcomes, other authors have studied different receptor areas: Jansson and Tisell, in subcutaneous abdominal adipose tissue [21], Kinnaert et al., in presternal subcutaneous region [22], Chou et al. and Monchik et al., in subcutaneous forearm tissue [8, 23], and Lieu et al., into the sternocleidomastoid muscle [24]. Since then, forearm musculature has not longer been considered the sole receptor area.

It has been reported that autotransplantation of parathyroid tissue should meet the following requirements: only recently removed parathyroid tissue should be transplanted, the implantation site should be easily accessible during

neck surgery, and, in case of recurrent hyperparathyroidism or infiltrating growth, part, or all, of the parathyroid tissue should be easily removed [21]. Many centers have abandoned cryopreservation because of a lack of success in reimplantation of cryopreserved tissue, and only use fresh tissue, if possible. In our study, we have evaluated patients with renal chronic disease who underwent total parathyroidectomy with intramuscular presternal autotransplantation. By resorting to this technique, we fulfilled the ideal requirements by using fresh tissue for transplantation in accessible graft area during neck surgery. Taking recurrence risk into account, this surgical approach revealed low levels of graft-dependent recurrence rates (6 recurrences in 66 patients), presenting feasible graft surgical removal under local anesthesia. It is worth noting that all recurrences occurred in patients under dialysis treatment. Therefore, the most important reason for recurrence concerns not to surgical approach itself, but long-lasting renal disease, once no recurrence was observed among kidney-grafted patients throughout extensive followup.

This study presents some limitations. One is concerned to unknown levels of vitamin D, once that measurements were not available in our service. Another limitation is related to peculiarities in the study group: that marked ill and long-lasting renal patients are a special group whose outcome would not be expected in current patients with renal chronic disease. Unfortunately, that severe illness observed in our patients is a rare condition. Third, we do not have, until present date, other studies with the same surgical approach so as to properly compare surgical results.

The ideal serum concentrations of intact PTH to be achieved after surgery remain controversial for patients with renal chronic disease, once neither adynamic bone disease nor high recurrence rate is intended [25]. Acknowledging that intact PTH levels are yet to be defined, we have reached intact PTH levels around 100 pg/mL in both groups (SHPT and THPT) and a low occurrence of definitive hypoparathyroidism (6,06%), thus showing interesting results with this surgical approach.

5. Conclusion

In conclusion, presternal intramuscular autotransplantation of parathyroid tissue is a feasible and safe surgical option in SHPT and THPT treatment, at least as effective as other surgical approaches.

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