Hypothesis: Presternal subcutaneous autotransplantation of parathyroid tissue after total parathyroidectomy for renal hyperparathyroidism could be at least as effective as intramuscular grafting, without its complications.

Design: Prospective study of a postoperative diagnostic method of monitoring intact parathyroid hormone (iPTH) levels among a cohort of surgical patients, without loss to follow-up.

Setting: Hemodialysis unit in a university hospital.

Patients: Twenty-five patients (17 women and 8 men) underwent total parathyroidectomy and presternal subcutaneous autotransplantation for renal hyperparathyroidism at Donostia Hospital, San Sebastián, Spain, between January 1, 2002, and June 30, 2004.

Main Outcome Measures: Evaluation of parathyroid graft function by measurement of serum iPTH levels at admission and 24 hours and 1, 3, 5, 15, 30, and 60 weeks after surgery.

Results: The mean±SD preoperative serum iPTH level was 1302±425 pg/mL; the iPTH level was undetectable in all patients 24 hours after surgery. Subsequent mean±SD iPTH levels obtained were 14±10 pg/mL after 1 week, 54±1 pg/mL after 5 weeks, 64±9 pg/mL after 15 weeks, 77±8 pg/mL after 30 weeks, and 106±21 pg/mL after 60 weeks. Autotransplanted parathyroid tissue appears to be adequately functional at week 5 (criterion level of adequate functioning, 50 pg/mL).

Conclusions: Presternal subcutaneous autotransplantation after total parathyroidectomy for renal hyperparathyroidism may be an alternative to avoid musculus brachialis grafting and its complications. Our functional results compare favorably with the published data on other surgical techniques for the treatment of renal hyperparathyroidism. Long-term follow-up of this series is planned.

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Since the first report of human parathyroid gland transplantation in 1975 by Wells et al., several techniques have been used to manage renal hyperparathyroidism (RHP). These include subtotal parathyroidectomy; total parathyroidectomy (TPT); TPT with cervical autotransplantation; TPT with musculus brachialis autotransplantation; TPT with antebrachial; abdominal; or presternal subcutaneous autotransplantation; and TPT without autotransplantation for patients with secondary RHP.

Outcomes of these procedures are problematic because of poor function, recurrence, and surgical difficulties at reoperation. To avoid these problems, subcutaneous parathyroid grafting has been performed. Resection of hypertrophied grafts is associated with musculus brachialis recurrences (Figure 1), resulting in iterative surgery and late forearm motion sequelae. Based on the results of a small study, recurrences are easy to treat when disease recurs after subcutaneous implantation, although the follow-up period in this study was short and did not fully evaluate graft function. Subcutaneous implantation has been performed in the forearm, abdomen, and sternum, although doubts persist about viability of the transplanted tissue.

Parathyroid glands are normally entirely or partially surrounded by fatty tissue. Therefore, we postulated that late results of subcutaneous autotransplantation of parathyroid tissue into their normal tissue environment in patients with RHP should be at least as good as those associated with intramuscular grafting, without its local complication risks.

In the setting of TPT for RHP, we evaluated parathyroid graft function after presternal subcutaneous autotransplantation. Parathyroid transplantation on
muscular structures, usually in the forearm, is the standard surgical procedure to treat RHP. Parathyroid transplantation after TPT should not only restore adequate parathyroid function in patients receiving hemodialysis but also prevent complications associated with transplanted tissue. All abnormal parathyroid tissue must be removed at the initial operation to normalize the levels of intact parathyroid hormone (iPTH) in patients with RHP.

The objective of the present study was to demonstrate a postoperative diagnostic method of monitoring iPTH levels among a cohort of patients who underwent presternal subcutaneous autotransplantation of parathyroid tissue after TPT. We then evaluated whether our functional results compare favorably with those reported for other surgical techniques used in the treatment of RHP.

METHODS

DESIGN AND SETTING

The design was a prospective single-blinded efficacy study monitoring iPTH levels among a cohort of surgical patients. The setting was a university referral center with an endocrine surgery center, an endocrine biochemistry laboratory, and a hemodialysis unit.

The ethics committee of Donostia Hospital, San Sebastián, Spain, approved the study, and all patients provided signed informed consent for the procedure. The study methods did not increase the morbidity or duration of the surgical procedure.

PATIENTS

Twenty-five patients (17 women and 8 men; mean ± SD age, 51.5 ± 6.9 years) who were treated in the hemodialysis unit of the Department of Nephrology of Donostia Hospital between January 1, 2002, and June 30, 2004, having the diagnosis of RHP secondary to chronic renal failure were included in the study. No patient was lost to follow-up. The mean ± SD duration of hemodialysis among the patients was 85.0 ± 13.3 months. Patients awaiting renal transplantation were excluded from the study.

On average, serum calcium levels were slightly higher than normal in this group of patients. All patients were treated with cholecalciferol and phosphate-binding compounds. None received aluminum-containing medications. None of the patients had diabetes mellitus. All patients had severe RHP (iPTH levels, >500 pg/mL). The criteria for the diagnosis of RHP were hypercalcemia (mean ± SD calcium level, 10.4 ± 0.6 mg/dL [2.6 ± 0.2 mmol/L]; reference range, 8.1-10.2 mg/dL [2.03-2.55 mmol/L]) and increased iPTH levels (1302 ± 425 pg/mL; reference range, 10-65 pg/mL). The mean ± SD preoperative creatinine level was 4.0 ± 2.3 mg/dL [354 ± 203 µmol/L]; reference range, 0.5-1.1 mg/dL [44-97 µmol/L]. Parathyroid gland enlargement was demonstrated by ultrasonography in all patients. In some patients, technetium Tc 99m sestamibi imaging or computed tomography was performed.

INDICATIONS FOR SURGERY

Surgery was performed in all patients after prophylactic treatment with calcium and cholecalciferol supplements had failed, causing hypercalcemia and a high serum phosphorus level. Patients underwent excision of all visible parathyroid glands, with subcutaneous implantation of autologous parathyroid tissue in the frontal lower middle third of the sternum. The number of parathyroid glands removed during the procedures was determined by microscopic examination of all resected specimens. Parathyroid glands showing macroscopically diffuse hyperplasia were preferentially used for grafting.

SURGICAL PROCEDURE

All procedures were performed by the same surgical team. Patients were admitted to the hospital on the day before or the day of surgery. Surgery was performed under general anesthesia, with orotracheal intubation. A Kocher incision 8 to 10 cm long was made over the anterior aspect of the neck 2 cm above the sternum notch. All 4 parathyroid glands were removed along with the thymus. For frozen section confirmation of
parathyroid tissue, 3½ parathyroid glands were submitted to the pathology department. The surgical team was notified as soon as the frozen section results were available. Twenty 1-mm³ fragments were prepared from the preserved parathyroid gland half for subcutaneous autotransplantation (Figure 2).

ALIQUOTS

All aliquots were obtained from a peripheral vein. Eight aliquots were obtained from each patient according to the following protocol: 1 aliquot each at hospital admission, 24 hours after surgery, and 1, 3, 5, 15, 30, and 60 weeks after surgery. For every sample, albumin, protein, iPTH, calcium, phosphorus, magnesium, and alkaline phosphatase levels were assayed.

LABORATORY ASSAYS

Levels of serum iPTH were measured in all patients using an Elecsys electrochemiluminescence assay (Roche Diagnostics GmbH, Mannheim, Germany). The iPTH measurements were obtained 24 hours and 1, 3, 5, 15, 30, and 60 weeks after surgery. For albumin, protein, calcium, magnesium, and alkaline phosphatase levels, a standard Corning analyzer (Corning, NY) was used. The mean half-life of iPTH is about 3 to 5 minutes,¹²-¹⁴ and a reduction to undetectable levels was observed in all patients 24 hours after surgery.¹²-¹⁵

MAIN OUTCOME MEASURES

The serum iPTH levels were measured at admission and 24 hours after surgery. Six additional measurements were obtained 1, 3, 5, 15, 30, and 60 weeks after surgery.

HISTOLOGIC STUDIES

All of the parathyroid glands were histologically examined by the same senior pathologist. The characteristics of the parathyroid glands were defined according to criteria established by Wallfelt et al.¹⁶

STATISTICAL AND DATA ANALYSES

Linear regression analysis was used to study the relationship between serum iPTH levels and time after surgery. The postoperative diagnostic method of monitoring iPTH levels provided time-dependent data for analysis.

SURGICAL PROCEDURE

Four parathyroid glands were removed from each patient. No supernumerary glands were observed in
this series. Pathological examination did not demonstrate additional parathyroid glands in any excised thymus.

SERUM iPTH LEVELS

The mean±SD preoperative iPTH level was 1302±425 pg/mL (range, 493-2160 pg/mL) (Figure 3). After TPT and presternal subcutaneous autotransplantation, iPTH was undetectable in all patients 24 hours after surgery (Figure 4). The criterion level of adequate parathyroid graft functioning was set at 50 pg/mL. During the follow-up period, the mean±SD iPTH levels were as follows: 14±10 pg/mL (range, 6-36 pg/mL) after 1 week, 54±1 pg/mL (range, 43-74 pg/mL) after 5 weeks, 64±9 pg/mL (range, 11-89 pg/mL) after 15 weeks, 77±8 pg/mL (range, 25-104 pg/mL) after 30 weeks, and 106±21 pg/mL (range, 65-143 pg/mL) after 60 weeks. Autotransplanted parathyroid tissue appeared to be adequately functional at week 5. One patient developed HP (iPTH level, <10 pg/mL, with a normal or low serum calcium concentration), with recovery by week 60.

The most commonly used procedures to treat RHP are subtotal parathyroidectomy and combined TPT with forearm intramuscular implantation of parathyroid tissue. Both techniques leave a small amount of abnormal parathyroid tissue in the patient. Because chronic renal failure persists after surgery, this glandular tissue is continuously stimulated, and RHP may recur. Some authors advocate TPT without grafting to prevent these recurrences, arguing that the absence of iPTH has no significant effect on the bones of patients receiving hemodialysis if the patients are treated with calcium and cholecalciferol supplements.14,15 These conclusions are questioned by other investigators.16 The ideal serum concentration of iPTH among patients with uremia is unknown, with the advocated levels varying from 75 to 175 pg/mL.17-19 As some secretion of iPTH seems necessary, we perform autotransplantation of parathyroid tissue, but instead of transplanting the parathyroid gland fragments into a muscle (where subsequent resection can be difficult), we recommend that the grafts be implanted subcutaneously in the frontal lower middle third of the sternum, where they can be easily located.

Figure 4. Evolution of intact serum parathyroid hormone (iPTH) levels after total parathyroidectomy and presternal subcutaneous autotransplantation. The criterion level of adequate parathyroid gland functioning is shown as indicated by the dotted line at 50 pg/mL.
and excised under local anesthesia in the event of a recurrence.11

Excision of all abnormal parathyroid tissue is essential for adequate functioning of these grafts. In the present study, all patients had 4 parathyroid glands removed, and no additional parathyroid glands were found in this series. Late development of hypercalcemia has been reported in 5.8% to 6.6% of patients after subtotal parathyroidectomy and in 6.6% to 10.7% of patients after TPT and intramuscular autotransplantation.20,21 and reoperation has been reported in 6% to 8% of patients after subtotal parathyroidectomy and in 5% to 15% of patients after TPT and intramuscular autotransplantation.22,23 In a study by Higgins et al.,14 parathyroid grafts had been excised 5 years after surgery in 30% of patients who had undergone TPT and intramuscular autotransplantation. Most of these series22,21 included patients in whom fewer than 4 parathyroid glands had been excised during surgical exploration of the neck.

In a prospective randomized clinical trial with a mean follow-up of 40 months, Rothmund et al20 compared outcomes in 20 patients who underwent subtotal parathyroidectomy vs 20 patients who underwent TPT and intramuscular autotransplantation. Development of hypercalcemia was less frequent and no reoperation was required among the patients who underwent TPT and intramuscular autotransplantation.

In vitro investigations25,26 comparing the functioning of cells from parathyroid nodules with that of cells from areas of parathyroid hyperplasia suggest that grafting of nodular tissue should be avoided to prevent recurrence. Macroscopic evaluation of nodularity seems adequate for selection of parathyroid glands for autotransplantation. Gagné et al27 reported that patients with autografts of nodular tissue had higher recurrence rates (with recurrence defined as an iPTH level higher than twice the upper normal limit) than those with autografts with diffuse hyperplasia after subtotal parathyroidectomy or combined TPT and intramuscular grafting. These conclusions were not supported by the results of Kinnaert et al.,7 who did not observe a relationship between parathyroid autograft function and histologic findings based on examination of surgical specimens. Reoperation rates were similar among all patients, and iPTH levels were not significantly higher among patients with nodular autografts. However, their findings may have been affected by the longer follow-up of the patients with nodular autografts compared with the patients with grafts with diffuse hyperplasia.

Other authors17,28,29 have shown that a significant proportion of patients with uremia who are treated by maintenance hemodialysis develop RHP. Therefore, the discrepancies among the studies discussed herein cannot be attributed only to differences in surgical technique. Adequate functioning of parathyroid grafts depends on multiple other factors, including prescribed therapy and patient compliance.

Because there is no consensus concerning adequate iPTH levels in patients with chronic renal failure, RHP was arbitrarily defined in this study as an iPTH level less than 20 pg/mL. Admittedly, this definition does not include all patients with an iPTH level that is insufficient to maintain a normal bone turnover, but it allows comparison with previously published data. In our study, the prevalence of RHP (iPTH level, <20 pg/mL, with a normal or low serum calcium concentration) was 100% (25/25) after week 1, but iPTH levels returned to normal in all patients by week 5, except for 1 patient who recovered by week 60.

In the present study, none of the patients received aluminum–containing phosphate binders as part of their treatment before surgery. This type of medication is no longer administered in our unit to patients undergoing hemodialysis. Therefore, it was not necessary to investigate the possibility of aluminum intoxication, which is known to inhibit parathyroid gland secretion.28 Furthermore, Berland et al29 found that the aluminum content of parathyroid glands was similar in patients with or without bone aluminum deposits. Moreover, because RHP was observed in patients who had not been exposed to aluminum and tended to be more frequent in women, other factors (technical, hormonal, or both) could be responsible for the lack of secretion of the grafts.

Because of a slow progressive increase in serum iPTH levels over time, patients may require excision of their transplanted autografts. This is not a matter of concern, as the procedure is technically straightforward after pre-sternal subcutaneous autotransplantation. In conclusion, the late results of pre-sternal subcutaneous autotransplantation after TPT compare favorably with published data on other forms of surgical treatment of RHP.20,22 The present results warrant further use of this procedure. Long-term follow-up in this series is planned to confirm this hypothesis.

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Correspondence: Miguel Echenique-Elizondo, MD, PhD, Department of Surgery, Basque Country University School of Medicine, 105 Paseo Doctor Beguiristain, 20014 San Sebastián, Spain (gepecelmi@sc.ehu.es).

REFERENCES


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