Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Percutaneous ethanol injection therapy in post-transplant patients with secondary hyperparathyroidism

Walter G. Douthat,[1] Santiago E. Orozco,[2] Pablo Maino,[2] Gabriela Cardozo,[1] Javier de Arteaga,[1] Jorge de la Fuente,[1] Carlos R. Chiurchiu[1] and Pablo U. Massari[1]

1 Bone and Mineral Metabolism Section, Renal Service, Hospital Privado-Centro Médico de Córdoba, Postgraduate School of Nephrology, Catholic University of Córdoba, Córdoba, Argentina
2 Department of Radiology, Hospital Privado-Centro Médico de Córdoba, Córdoba, Argentina

Keywords
percutaneous ethanol injection therapy, renal osteodystrophy, renal transplant, secondary hyperparathyroidism.

Correspondence
Walter Guillermo Douthat, Bone and Mineral Metabolism Section, Renal Service, Hospital Privado – Centro Médico de Córdoba, Naciones Unidas 346 (5016) Córdoba, Argentina. Tel.: (0054 - 351) 4688230; fax: + (0054 - 351) 4688844; e-mail: wdouthat@hospitalprivadosa.com.ar

Received: 17 April 2007
Revision requested: 30 April 2007
Accepted: 28 July 2007

doi:10.1111/j.1432-2277.2007.00545.x

Summary

Persistent hyperparathyroidism is frequent in postrenal transplant patients. Percutaneous ethanol injection therapy (PEIT) is an alternative for treatment of patients with secondary hyperparathyroidism but it was not described in post-renal transplant patients. We report our experience with PEIT to control hyperparathyroidism in the post-transplant period. We performed PEIT under ultrasonographic guidance and local anesthesia in eight patients because of persistent secondary hyperparathyroidism after renal transplantation. Indications for PEIT were: high intact parathyroid hormone (iPTH) levels with hypercalcemia, hypophosphatemia, osteopenia and/or bone pain. All patients had at least one visible parathyroid nodule by ultrasonography. Biochemical assays were performed immediately before PEIT, between 1 and 7 days after last PEIT, and a mean of 8.0 ± 2.8 months after PEIT. Serum iPTH and calcium levels decreased significantly after treatment and remained unchanged until final control. Serum iPTH decreased from 286.9 ± 107.2 to 154.6 ± 42.2 pg/ml ($P < 0.01$) after PEIT (percentual reduction 36.5 ± 9.5%). This response was significantly correlated to total ethanol volume used (r: 0.94, $P < 0.0001$). Hypercalcemia disappeared in six of eight patients treated. Only minor complications were registered. There were no changes in renal function related to the treatment. Our findings show that PEIT is a useful and safe alternative for patients with persistent post-transplant secondary hyperparathyroidism.

Introduction

Secondary hyperparathyroidism and its related complications are frequently observed after renal transplantation [1–3]. Successful renal transplantation does not necessarily warrant reversibility of parathyroid over activity [4]. Persistence and severity of post-transplant hyperparathyroidism is related to pretransplant PTH levels, parathyroid glands size and to nodular appearance [4,5]. Post-transplant hyperparathyroidism is characterized by hypercalcemia, hypophosphatemia, soft tissue calcifications, bone pain, fractures and renal function impairment as well [6–9]. Parathyroidectomy is indicated when patients are symptomatic and complications are present [10,11].

Percutaneous ethanol injection therapy (PEIT) is an alternative therapy to surgery for those patients with chronic renal failure and secondary hyperparathyroidism that are resistant to medical therapy. Successful nodule destruction has been obtained in dialysis patients [12–15], nevertheless its use has not yet been described in postrenal transplantation.

We report our experience with PEIT in renal transplant patients with secondary hyperparathyroidism in whom medical therapy failed or was contraindicated.

Methods

Eight patients with persistent postrenal transplant hyperparathyroidism who did not respond to medical therapy were treated with PEIT.

All patients, three women and five men (mean age 44.1 ± 3.7 years), gave their informed consent to the procedure.

Patients were on dialysis before transplantation for 77.3 ± 20.0 months. They had received a kidney transplant 25.1 ± 10.0 months (range 6–92) before the procedure and were followed 8.0 ± 2.8 months (range 1–25) after last PEIT session (Table 1). This time was the last information of follow-up available for each patient and corresponds to the last biochemical sample (final).

The underlying causes of end-stage renal disease (ESRD) were chronic glomerulonephritis ($n = 4$), postpartum renal failure ($n = 1$), chronic pyelonephritis ($n = 1$) and unknown ($n = 2$).

Six patients received a graft from cadaveric donors and two from related living donors. Post-transplant immunosuppressive therapy consisted of cyclosporine, glucocorticoids and mycophenolate mofetil. No episodes of acute rejection were registered before and throughout the study. At the time of PEIT all patients had normal renal function with a mean serum creatinine of 1.36 ± 0.70 mg/dl (120.2 ± 61.8 μmol/l).

Inclusion criteria for PEIT treatment were: persistent postrenal transplant hyperparathyroidism [PTH levels higher than 100 pg/ml (ng/l)], lack of responsiveness to medical therapy, discontinuation of calcitriol therapy due to hypercalcemia [serum calcium >10.5 mg/dl (2.62 mmol/l)], and/or hypophosphatemia [serum phosphorous <2 mg/dl (0.65 mmol/l)] and significant bone decalcification. The presence of at least one visible parathyroid nodule by ultrasonography was also an essential inclusion criteria.

Biochemical determinations

Biochemical assays were performed immediately before the first PEIT session (basal) and between day 1 and 7 after the last PEIT session (PostPEIT). The last biochemical assessment obtained postPEIT, was considered as final control (Table 1). Serum creatinine, calcium, phosphorus and alkaline phosphatase were measured with autoanalyzer (Hitachi 917: Hitachi, Ltd, Tokyo, Japan), and iPTH was determinated by electrochemiluminiscence (Nichol's Institute, San Juan Capistrano, CA, USA).

PEIT technique

Percutaneous ethanol injection therapy was performed under ultrasonographic guidance, in an ambulatory facility. Nodular volume and size of all glands treated with PEIT were larger than 0.1 cm^3 as calculated by ultrasonographic evaluation of their longest axis. All injections were administered by the same qualified interventional radiologist. A 95% ethanol solution was used for PEIT with total alcohol volume calculated to be at least the same of the nodule. A modified needle for ethanol injection with small side holes (3.5 mm) that can be easily recognized under ultrasonography was used in all PEIT sessions. Local anesthesia with lidocaine was used. One or more injections were performed in each session, according to the anatomic characteristic of the glands.

Percutaneous ethanol injection therapy was made into the largest parathyroid nodule. For those patients with more than one large parathyroid nodule, a second injection was performed. Successful nodule destruction was considered when the enlarged gland was no longer visible by ultrasonography after last PEIT session.

Major and minor complications related to the proceeding were recorded for each patient.

Table 1. Individual mineral metabolism markers, renal function and time of follow-up.

	iPTH (pg/ml)			sCa (mg/dl)			SPi (mg/dl)			MDRD (ml/min)			Time from last PEIT to last control (Final) (mo)
Patient	Pre PEIT	PostPEIT	Final	Pre PEIT	PostPEIT	Final	Pre PEIT	PostPEIT	Final	Pre PEIT	PostPEIT	Final	
1	400	305	176	12.3	11.4	11.6	1.5	2.3	2.2	59.9	53.0	58.5	13
2	125	85	85	10.8	10.2	10.2	2.5	3.2	3.2	67.2	68.9	66.9	1
3	150	25	70	14.4	9.8	9.2	2.2	2.1	2.6	64.5	50.4	77.9	11
4	167	111	134	9.8	9.6	10.2	3.7	3.4	3.8	40.6	46.4	45.5	6
5	133	81	115	11.6	10.9	10.0	2.9	3.0	2.4	57.4	59.8	61.4	25
6	1000	354	347	11.0	10.4	10.4	3.7	2.9	3.9	40.2	40.0	41.1	2
7	220	200	98	10.7	9.7	10.4	2.9	2.6	2.6	37.2	42.3	42.8	6
8	192	186	290	12.1	11.0	11.6	1.7	1.7	2.0	70.9	72.4	67.5	3

PEIT, percutaneous ethanol injection treatment; iPTH, intact parathyroid hormone; sCa, total serum calcium; sPi, serum inorganic phosphate; MDRD, modification of diet in renal disease equation.

Statistical analysis

Results are expressed as mean ± SE. Statistical analysis for continuous variables was performed with Wilcoxon non-parametric test. Correlations between variables were calculated according to Pearson's coefficient. A value of $P < 0.05$ was considered as significant.

Results

A total of 1.38 ± 0.26 nodules were injected in a mean of 1.38 ± 0.18 sessions per patient (Table 2). Patients 1, 3, 4, 5, 6 and 7 had only one visible nodule by ultrasonography, patient 2 had two nodules, and patient 8 had three, but only two of them were injected. Total nodule size per patients was 1.03 ± 0.46 cm^3, and mean size per nodule was 0.68 ± 0.19 cm^3 (range 0.06–1.93). Mean ethanol volume used per patients was 3.15 ± 0.34 cm^3 (Table 2).

Basal hypercalcemia [>10.5 mg/dl (2.62 mmol/l)] was present in seven patients. Only one patient (number 4) had a normal serum calcium [9.8 mg/dl (2.44 mmol/l)] with intact parathyroid hormone (iPTH) of 167 pg/ml (ng/l), severe bone pain, osteoporosis and without response to medical therapy (Table 1).

Patient 8 did not complete PEIT because of technical difficulties and was parathyroidectomized several months later because of persistent hypercalcemia and hypophosphatemia (Table 1).

A significant decrease of iPTH (286.9 ± 107.2 to 154.6 ± 42.2 pg/ml, $P < 0.01$) and serum calcium (11.4 ± 0.5 vs. 10.3 ± 0.2 $P < 0.01$) occurred immediately after PEIT. The decrease of both markers persisted 8.0 ± 2.8 months after PEIT (146.4 ± 35.9 pg/ml and 10.3 ± 0.3 mg/dl respectively) (Fig. 1). Moreover, a significant decrease in alkaline phosphatase was registered. A tendency to increase serum phosphate levels were observed throughout the follow-up after PEIT (Fig. 1) but it did not reach statistically significant level.

Mean percentage decrease of iPTH levels after last PEIT session was 36.5 ± 9.5%, and it displayed a strong correlation with total ethanol volume used (Fig. 2).

There were no significant differences in renal function-estimated according MDRD- pre and postprocedure (Table 1).

Table 2. Data of the procedure (PEIT) and ultrasonographic characteristics of nodules.

Characteristics	Mean ± SE
Nodules/patient (*n*)	1.38 ± 0.26
Injections/patient (*n*)	1.38 ± 0.18
Ethanol volume/patient (cm^3)	3.15 ± 0.34
Total nodule size/patient (cm^3)	1.03 ± 0.46
Size/gland (cm^3)	0.68 ± 0.19

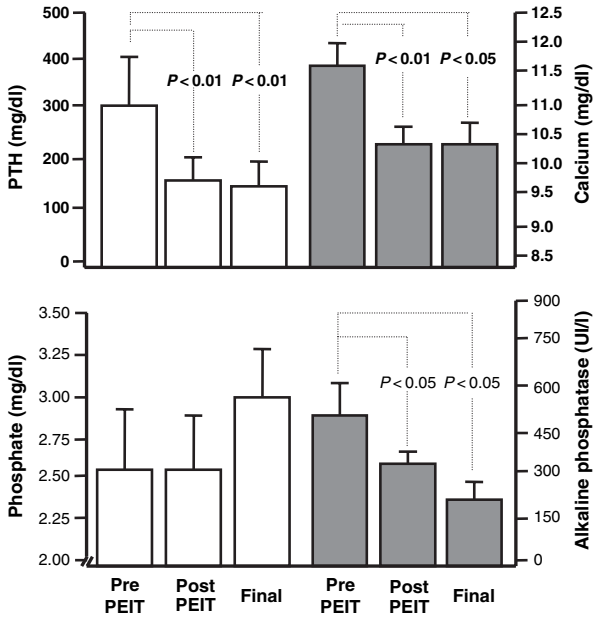

Figure 1 Intact parathyroid hormone, calcium, phosphate and alkaline phosphatase levels.

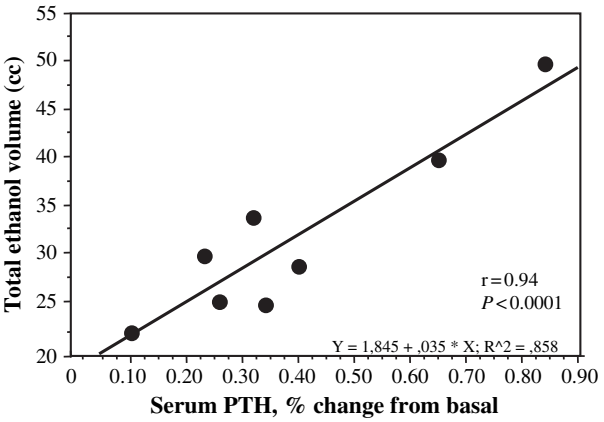

Figure 2 Correlation between percentual reduction of intact parathyroid hormone and total ethanol volume.

Minor complications were registered in some patients. Four patients experimented neck discomfort that ceased immediately after the procedure, and one patient developed transient dysphonia.

Discussion

Percutaneous ethanol injection therapy is an easy and safe technique to control moderate and severe secondary hyperparathyroidism in dialysis patients, however this technique was never described after renal transplantation.

This study demonstrated for first time that selective destruction of nodular parathyroid glands with ethanol injection is a useful and safe treatment for post-transplant patients with persistent secondary hyperparathyroidism resistant to medical therapy.

Secondary hyperparathyroidism is a frequent complication in this period [1–3]. In our experience, almost half of patients after 2 years postrenal transplantation, maintain PTH levels above normal, 15% had hypercalcemia and 21% hypophosphatemia (data not published). It has been related to abnormal secretion of PTH because of incomplete regression of hyperplasic parathyroid glands cells [4,5]. Hyperparathyroidism often induces moderate to severe hypercalcemia [6]. Post-transplant hypercalcemia remains a difficult disorder to manage, inducing graft dysfunction and favoring dehydration, nephrocalcinosis, nephrolithiasis and osteopenia. One of the proposed mechanisms for hypercalcemia is a better bone tissue response to PTH. This decrease in PTH resistance is due to an improvement of the uremic millieu that increase calcitriol levels thus prevent hyperphosphatemia.

In patients with ESRD and hyperparathyroidism, frequently vitamin D derivatives are used to block PTH production and secretion, thus blocking the secondary increase in calcium and phosphorus levels. At variance, in post-transplant patients Ca × P products may not be elevated despite high levels of iPTH because of the presence of renal function (diuresis) promoting both phosphaturia and hypophosphatemia [9].

Medical treatment for patients with ESRD and bone disease due to secondary hyperparathyroidism have recently been developed. However, medical management remains problematic in a huge number of patients due to lack of responsiveness to therapy [16]. Surgical parathyroidectomy for these patients usually results in an immediate reduction in PTH levels, as well as clinical and histological bone improvement in the short and long term [17].

Since the early 1980s, PEIT has been proposed as a less invasive alternative to parathyroidectomy [14]. The basis of this therapy is that enlarged parathyroid glands with nodular hyperplasia are destroyed selectively by ethanol injection [12–15]. We recently reported in dialysis patients a significant decrease in PTH, with improvement in serum calcium, phosphate and Ca × P product. These results were significantly correlated to PTH levels and to nodule volume [12]. ESRD patients on dialysis, with large nodule volume and very high PTH levels, obtained the better results after PEIT [12].

In the past years, our approach to treat hyperparathyroidism in the postrenal transplantation period had been conservative. Surgery was indicated in those cases unresolved 1 year after transplantation taking into account the iPTH levels. Nevertheless, parathyroidectomy is too invasive for patients with mild to moderate alterations in mineral parameters. In this setting, an easy, inexpensive and little invasive treatment as PEIT could be preferred. On the other hand, parathyroidectomy has demonstrated to affect negatively renal function [18] something that was not found with PEIT. Drugs such as cinacalcet could be also useful in these patients although it is not yet available in Latin-American countries and in many others parts of the world [19,20].

In this study, all treated patients had at least one clinical or metabolic complication related to hyperparathyroidism such as hypercalcemia, hypophosphatemia, bone pain, fractures, bone abnormalities and lack of response to medical therapy. The patients experienced after PEIT, a significant decrease in serum calcium, iPTH and alkaline phosphatase during the follow up, reflecting an excellent bone response. Other parameters such as phosphate had a very impressive response as well. The levels increased and remained unchanged for a long time after PEIT (Figs 1 and 2).

Although this is a small series, show that patients with secondary hyperparathyroidism after renal transplantation could be successfully managed with PEIT. The technique offers the additional advantage of low cost, could be performed in out-patients basis, avoiding parathyroidectomy as well as the long-term consequences of hypercalcemia and high PTH levels.

In summary, PEIT is a useful alternative for the management of post-transplant hyperparathyroidism, inducing persistent and significant decrease in serum iPTH, with an improvement in the metabolic profile associated with bone disease in the post-transplant period.

Authorship

WGD: designed research, performed research, analyzed data, wrote paper. SEO: performed research. PM: performed research. GC: collected data. JDA: contributed important reagents. JDF: contributed important reagents. CRC: analyzed data, wrote paper. PUM: analyzed data, wrote paper.

Acknowledgements

This work was supported in part by Fundación Nefrológica de Córdoba. The authors thank Dr Kioshi Kurokawa for the kind supply of specially designed PEIT needles.

References

1. Massari P. Disorders of bone and mineral metabolism after renal transplantation. *Kidney Int* 1997; **52**: 1412.

2. Douthat W, Massari P, Cannata JB. Trastornos del metabolismo óseo y mineral en el trasplante renal. *Nefrología* 1994; **14**: 408.
3. Alsina J, Gonzalez M, Bonnin R, *et al.* Long-term evolution of renal osteodystrophy after renal transplantation. *Transplant Proc* 1989; **21**: 2151.
4. Messa P, Sindici C, Canella G, *et al.* Persistent secondary hyperparathyroidism after renal transplantation. *Kidney Int* 1998; **54**: 1704.
5. McCarron D, Muther R, Lenfesty B, *et al.* Parathyroid function in persistent hyperparathyroidism: relationship to gland size. *Kidney Int* 1982; **22**: 662.
6. Parfitt A. Hypercalcemic hyperparathyroidism following renal transplantation: differential diagnosis, management, and implications for cells population control in the parathyroid gland. *Miner Electrolyte Metab* 1982; **8**: 92.
7. Almond N, Kwan J, Evans K, *et al.* Loss of regional bone mineral density in the first 12 months following renal transplantation. *Nephron* 1994; **66**: 52.
8. Julian B, Laskow D, Dubovsky J, *et al.* Rapid loss of vertebral mineral density after renal transplantation. *N Engl J Med* 1991; **325**: 544.
9. Levi M. Post-transplant hypophosphatemia. *Kidney Int* 2001; **59**: 2377.
10. Schmid T, Muller P, Spelsberg F. Parathyroidectomy after renal transplantation: a retrospective analysis of long-term outcome. *Nephrol Dial Transplant* 1997; **12**: 2393.
11. D'alessandro A, Melzer J, Pirsch J, *et al.* Tertiary hyperparathyroidism after renal transplantation: operative indications. *Surgery* 1989; **106**: 1049.
12. Douthat W, Orozco S, de Arteaga J, *et al.* Treatment of refractory secondary hyperparathyroidism with ethanol injection: the importance of glandular volume. *Kidney Int* 2003; **63**(Suppl. 85): S101.
13. Fukagawa M, Kitaoka M, Tominaga Y, *et al.* Guidelines for percutaneous ethanol injection therapy of the parathyroid glands in chronic dialysis patients. *Nephrol Dial Transplant* 2003; **18**(Suppl. 3): 2.
14. Solbiati L, Giangrande A, Pra R, *et al.* Ultrasound-guided percutaneous fine-needle ethanol injection into parathyroid glands in secondary hyperparathyroidism. *Radiology* 1985; **155**: 607.
15. Fukagawa M, Kitaoka M, Tominaga Y, *et al.* Selective percutaneous ethanol injection therapy (PEIT) of the parathyroid in chronic renal dialysis patients-The Japanese strategy. *Nephrol Dial Transplant* 1999; **14**: 2574.
16. Fukagawa M, Fukuda N, Yi H, *et al.* Resistance of parathyroid cell to calcitriol as a cause of parathyroid hyperfunction in chronic renal failure. *Nephrol Dial Transplant* 1995; **10**: 316.
17. Stracke S, Jehle P, Sturm D, *et al.* Clinical course after total parathyroidectomy without autotransplantation in patients with end-stage renal failure. *Am J Kidney Dis* 1999; **33**: 304.
18. Schwarz A, Rustien G, Merkel S, *et al.* Decreased renal transplant function after parathyroidectomy. *Nephrol Dial Transplant* 2007; **22**: 584.
19. Block G, Martin K, de Francisco A, *et al.* Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Eng J Med* 2004; **350**: 1516.
20. Cunningham J, Danese M, Olson K, *et al.* Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int* 2005; **68**: 1793.

