



Renal hyperparathyroidism management after subtotal parathyroidectomy

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SUMMARY

Parathyroidectomy, in any of its forms, is considered an effective short-term treatment of renal hyperparathyroidism in patients who are not being controlled with drugs. Nevertheless, the outcome in the medium and long term of the various surgical procedures is still unclear and seems a controversial issue. We conducted a prospective study of 15 patients undergoing subtotal parathyroidectomy who were followed up for a period of 48 months after surgery. All patients were included in hemodialysis programmes. Elevated levels of parathyroid hormone which did not decrease with drug therapy recommended parathyroidectomy.

The aim of our study is to determine whether subtotal parathyroidectomy is an effective technique in the medium and long term.

As regards the results obtained, the levels of parathyroid hormone and calcemia remarkably decreased during the follow-up period, if compared to pre-surgery levels. The level of alkaline phosphatase also showed a reduction and the «hungry bone effect» was observed.

The phosphorus and Ca-P product levels only showed a significant reduction immediately after surgery but showed an increment from the first year after surgery onwards. Hemoglobin levels did not show any alteration after parathyroidectomy. In two patients we observed a relapse of hyperparathyroidism. The anatomopathological examination revealed nodular hyperplasia in most of the cases, including the two relapses.

Conclusion: *Subtotal parathyroidectomy is an effective surgical procedure in the medium-term treatment of renal hyperparathyroidism.*

Key words: *Secondary Hyperparathyroidism. Chronic renal failure. Parathyroidectomy.*

RENAL HYPERPARATHYROIDISM MANAGEMENT AFTER SUBTOTAL PARATHYROIDECTOMY

RESUMEN

La paratiroidectomía en cualquiera de sus modalidades se considera un tratamiento eficaz a corto plazo en el hiperparatiroidismo renal no controlado medi-

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camente. Sin embargo, no queda claro y parece controvertido el resultado a medio-largo plazo de las diferentes técnicas quirúrgicas. Realizamos un estudio prospectivo de 15 pacientes sometidos a paratiroidectomía subtotal. El seguimiento postoperatorio fue de 48 meses. Todos los pacientes estaban en programa de hemodiálisis. La indicación de paratiroidectomía fue una hormona paratiroidea elevada a pesar de tratamiento médico. El objetivo del estudio fue determinar si la paratiroidectomía subtotal es un procedimiento eficaz a medio-largo plazo. En cuanto a los resultados obtenidos, podemos decir que la paratohormona descendió con respecto a los niveles precirugía de forma significativa durante los años de seguimiento, al igual que ocurrió con la calcemia. La Fosfatasa Alcalina también se vio afectada considerándose el «efecto del hueso hambriento». Tanto el fósforo como el producto Ca-P sólo sufren un descenso significativo en el control postcirugía elevándose a partir del primer año de la intervención. La hemoglobina no se ve afectada por la paratiroidectomía. En dos casos hubo recurrencia del hiperparatiroidismo. El resultado anatomopatológico de la mayoría de los casos fue Hiperplasia Nodular, incluidos los casos de recurrencia.

Conclusión: La paratiroidectomía subtotal es una técnica quirúrgica efectiva en el tratamiento a medio plazo del hiperparatiroidismo renal.

Palabras clave: **Hiperparatiroidismo secundario. Insuficiencia renal crónica. Paratiroidectomía.**

INTRODUCTION

Secondary hyperparathyroidism (HPT) is the main cause of bone disease in patients submitted to hemodialysis¹. Its onset is early, and it is well-known that, among other factors, serum calcium levels decrease, vitamin D efficiency and serum phosphate levels increase as a consequence of renal function impairment are implicated in the pathogenesis. All this results in parathyroid gland increase due to cell hyperplasia and an increase of parathyroid hormone (PTH)³. At the beginning, this hyperplasia is diffuse but may become nodular, with a decrease in calcium and vitamin D cellular receptors that explains the lack of response to pharmacological treatment. Actually, the most frequent histological pattern in parathyroidectomy sections is nodular hyperplasia⁴⁻⁶.

Parathyroidectomy (PTX) becomes necessary for secondary HPT treatment when its management is not possible with dialysis and drug therapy. The biochemistry parameters that have been classically used to indicate a PTX are the following: high iPTH (the 1000 pg/mL level has been used), a calcium-phosphorus product higher than 70 mg²/dL² and a serum calcium level higher than 10.5 mg/dL^{7,8}.

The surgical procedures used (total PTX with autograft; total PTX without autograft; and subtotal PTX) have been and still are controversial. Currently, it

seems clear that all of them are effective, achieving HPT control and symptoms relieve, however, there is no uniform thinking about which is the best procedure for an intermediate-long term management^{9,10}.

The aim of this study is to analyze intermediate-term subtotal PTX outcomes in our dialysis patients presenting our experience with this technique.

PATIENTS AND METHODS

We studied 15 patients (9 women and 6 men) with chronic renal failure included in a hemodialysis program, and submitted to PTX between January 1996 and January 2002. Within this six-year period, 22 PTX were performed (4.5% of the total dialysis population in the same period). All procedures were done by the same surgeon at the Endocrine Surgery Unit of the General Surgery Department of our hospital. The procedure type was always subtotal PTX, excising the three largest glands and two thirds of the remaining one that was left in situ, in its original location. Exclusions from the study were seven patients for having a post-PTX follow-up time shorter than one year, 5 patients for death, and two patients for renal transplantation.

Mean age of the patients was 51.9 years (range: 38-64), with a mean renal replacement therapy du-

ration of 9.25 years (range: 1-17). The time elapsed from first elevated iPTH determination (> 200 pg/mL) and parathyroidectomy was 6 years (range: 2-12). The renal failure causes were: chronic glomerulonephritis (8 cases); nephroangiosclerosis (1 case); focal and segmentary glomerulonephritis (1 case); type II mesangiocapilar glomerulonephritis (1 case); interstitial nephropathy (2 cases); chronic pyelonephritis (1 case); Alport's syndrome (1 case). All presented secondary PTH with no response to medical treatment, and most of the cases had been treated with oral or intravenous vitamin D and with phosphorus chelation at the doses recommended in the literature prior to surgery. The lack of response to treatment was the indication for surgical treatment.

To diagnose HPT we used both biochemistry parameters and imaging tests such as cervical ultrasound and Tc-99m-sestamibi scintigraphy.

The revised analytical determinations were: iPTH, calcium, phosphorus, Ca-P product, alkaline phosphatase, and hemoglobin, measured immediately before and after surgery (24-48 hours after surgery), and at the second and fourth year after. In each patient, blood pressure was recorded with the same frequency.

At two years, we analyzed 14 patients, and at 4 years only 8, since one of them died and 6 have a post-PTX follow-up shorter than 4 years. The statistical method used has been a non-parametric test for paired data (Wilcoxon's test).

RESULTS

As expected, all biochemistry parameters studied after surgery present a significant change as compared to pre-surgical levels.

iPTH remains low during the four-year follow-up period ($p < 0.05$). Calcium remains at normal levels but requiring oral calcium and/or oral or intravenous vitamin D during the first post-surgery period. Only two out of 14 patients followed for two years after surgery required oral vitamin D, and

one out of 8 followed for 4 years still received vitamin D. Alkaline phosphatase significantly increases after surgery, remaining under control for the next follow-up years. By contrast, phosphorus and calcium-phosphorus product control is only achieved at the immediate post-surgery time, subsequently increasing and requiring treatment with phosphorus chelation in all reviewed cases. Hemoglobin decreases at post-surgical control, accordingly to the surgical background, but subsequently remains steady at slightly higher levels than the ones previous to surgery, but without any significant increase ($p > 0.05$). Erythropoietin and/or iron requirements are similar throughout all the follow-up period (table I).

Blood pressure levels do not significantly change after surgery, so that patients need to keep on taking antihypertensive treatment.

A 100% of cervical ultrasounds had intra-thyroid images congruent with thyroid gland enlargement.

Scintigraphy was done in 6 patients, being of diagnostic value in 5, and in one patient was reported as not valid for diagnosis.

The pathology study results were: nodular hyperplasia in 10 cases; diffuse hyperplasia in 3 cases, and a mixed pattern (nodular + diffuse) in two cases. With regards to size and weight of the surgical specimen, it was observed that in nodular hyperplasia the diameter varied between 10-40 mm, and weight between 0.4-2 g. In diffuse hyperplasia cases, the diameter was never greater than 10 mm (5-10 mm). All glands with nodular hyperplasia had more than one nodule, none of them being dominant with regards to the others. There was no relationship observed between glandular size and number of nodules. It is assumed that the gland left in situ has the same histopathological characteristics than the excised part of the same gland. In all cases, the study of all glands, included the partially excised one, coincided.

Of the 8 studied patients at 4 years, two (25%) had a recurrence. In one case, the patient presented an iPTH increase at the second year after surgery, with detection of a mediastinal parathyroid gland

Table I. Medians and interquartile ranges of the several biochemistry parameters

	iPTH (pg/ml)	Ca (mg/dl)	P (mg/dl)	FA (U/l)	Hb (g/ml)
Pre-surgery	1,310 (517)	10.2 (2.2)	6.6 (2.8)	579 (653)	11.1 (1.95)
Post-surgery	45.3 (115)*	9 (1.85)*	3.5 (2.1)*	686 (971)*	10.25 (142)*
2 years	58.1 (434.4)*	9.3 (1.1)	5.7 (2.85)	146 (107.25)*	11.95 (2.45)
4 years	109 (475.75)*	9.1 (1.28)*	6.4 (3.43)	210 (140.25)*	12 (2.97)

iPTH: intact parathyroid hormone. Ca: calcium; P: phosphorus; FA: alkaline phosphatase; Hb: hemoglobin. *Value vs. Pre-surgery $p < 0.05$.

with MIBI scintigraphy. The other case had a constantly elevated iPTH (> 200 pg/mL), being resubmitted to surgery at the 4th year for having elevated iPTH levels (> 1000 pg/mL) not controlled with medical treatment. The remaining patients presented iPTH levels < 200 pg/mL throughout the four-year study. In the two recurrent cases, the pathology result was nodular hyperplasia. In the recurrent case, nodular hyperplasia was observed in the remaining parathyroid gland that was re-excised.

DISCUSSION

Secondary HPT management must be started from early renal failure stages using the necessary means to keep calcium and phosphorus levels within a normal range. Once on dialysis, it is essential the use of a low-phosphorus diet, chelating agents, dialysis baths with calcium according to dietary calcium intake or intake of calcium chelating agents, adding oral or intravenous vitamin D as needed^{11,12}. The indication for surgical treatment is done when clinical/laboratory control is not achieved with previous measures.^{2,13} There are studies in which a PTX rate decrease has been observed due to advances in medical treatment; if this is the case, it might happen the same with recurrence rates^{14,15}. It might be that in the near future the new phosphorus chelating agents, calcium-mimetics, and the new vitamin D analogs will allow renal HPT control and, thus, PTX will be rendered unnecessary. In any case, nowadays the surgical treatment is still needed when medical therapy is insufficient.

PTX prevalence in our dialysis population during the time period in which surgical procedures were done is 4.5%, similar or somewhat lower to that reported in European studies with much greater number of patients and greater time on dialysis^{14,16}. The most large PTX series published in Spain is by Dr. Joffré, with 148 procedures done throughout 12 years. In most of the cases a total PTX with auto-graft was performed, and in 19 patients only 2 or 3 glands were identified in the cervical region that were excised without auto-graft. In 12 of these cases there was HPT recurrence (PTH < 750 pg/mL) although in 6 cases it was due to a mediastinal gland that had been unnoticed. This group would compare, with some differences, with ours of subtotal PTX. We found two recurrences at 4 years, one of which was due to a mediastinal adenoma.

After evaluating the results obtained, we appreciate that subtotal PTX is effective in the short and intermediate terms, achieving control of biochemi-

cal parameters. We have not observed severe hypocalcaemia in the immediate post-surgical period, probably due to the early implementation of intravenous calcium or vitamin D treatment. We do not observe hypocalcaemia during the follow-up time either. Some authors report that post-surgical hypocalcaemia incidence is higher when total PTX without auto-graft is performed, being similar with total PTX with auto-graft and in subtotal PTX.^{13,17} The latter is unclear since there are reports on the higher hypocalcaemia incidence with total PTX with auto-graft than with subtotal PTX².

Phosphorus management still is an issue in renal patients with parathyroidectomy, its levels normalizing only in the immediate post-surgical period, subsequently increasing. One year after surgery, virtually all patients presented phosphorus levels ≥ 5 mg/dL. This fact obliges to reestablish the treatments administered before surgery to achieve normal phosphorus serum levels and to prevent this way secondary HPT recurrence due to phosphorus-induced stimulation of parathyroid remnants. In Joffré's series an adequate phosphorus management was achieved in spite of the fact that within 5 years a certain number of patients had redeveloped HPT, as indicated by PTH results of 249 ± 480 pg/mL in 69 patients.

The surgical procedure used in our hospital for excision of thyroid glands was in all the cases subtotal parathyroidectomy, independently of patient's characteristics (age, inclusion or not in the transplantation waiting list). The theoretical advantage of total PTX with auto-graft over subtotal PTX is the avoidance of surgical neck examination in the event of recurrence^{2,18}, although this technique involves a greater risk for secondary hypoparathyroidism than subtotal PTX^{19,20}. One should keep in mind that the cause of recurrence might be a glandular remnant in the cervical area, an ectopic gland, and sometimes the grafted tissue itself, which forces the differential diagnosis to locate the real origin of the recurrence^{2,21}. This is not always an easy task and is partially avoided by subtotal PTX. On the other hand, auto-graft excision is usually difficult since the parathyroid tissue infiltrates the muscular layers.^{10,13} Recently, a surgical procedure has been described by which a piece of the non-excised thyroid gland is made superficial lying subcutaneously while preserving its vascular pedicle²². Another study has been published in which a pre-selected parathyroid tissue is intrasurgically auto-grafted by means of an stereomagnetizer that allows visualizing tissue with more fat cells and, thus, less proliferative²³. According to some authors^{5,8}, total PTX without auto-graft would be indicated in advanced age cases that are

no candidates to renal transplantation and in those that have recurrent HPT, recommending criopreservation of thyroid tissue in the case of a future need of auto-graft for hypocalcaemia. In this later case, total PTX with auto-graft is also indicated, with an option for criopreservation, especially in patients that may be submitted to renal transplantation, due to the risk for hypocalcaemia. On the other hand, by maintaining almost inexistent iPTH levels, total PTX may favor the development of adynamic bone disease and vascular calcifications^{5,24}. In our series, there was 1 case with a PTH level < 30 pg/dL at 4 years of follow-up. In the study by Dr. Joffré, approximately within 7 years 21 patients had PTH levels < 30 pg/dL.

It was not considered necessary to perform a bone biopsy before PTX since aluminum serum levels were normal and there was no suspicion of aluminum-induced bone disease.

The imaging tests used (cervical ultrasound and Tc-99m-sestamibi scintigraphy) may be considered quite reliable to confirm parathyroid glands enlargement, being easy to perform. Besides, in recurrent cases, scintigraphy is quite useful for localizing ectopic areas of parathyroid gland that usually are only diagnosed after PTX. There are studies that consider that imaging studies are only useful in recurrent cases since the indicated practice would be excision of the parathyroid glands at their usual location straightforward^{2,8}.

The most frequent pathology diagnosis in our series was nodular hyperplasia. It seems that this histological pattern is involved in a higher disease recurrence rate²⁵. Similarly to the results obtained by others^{6,26}, our two recurrent cases presented this pattern in the pathology examination. By contrast, there seems to be no relationship between the type of surgery and disease recurrence⁸. In one of our recurrent cases, the cause was the existence of thyroid gland at an ectopic location (mediastinal), and not hyperplasia of the remnant gland spared at surgery.

This study represents the analysis of our Nephrology Department and has the drawback of the limited number of patients, so that the outcomes may be debatable. However, we believe that subtotal PTX is an effective method to control secondary HPT in the short-intermediate term, but we cannot affirm so in the long term. It is foreseeable that due to the permanent uremia state and the difficult phosphorus management, disease recurrence may be inevitable. We consider subtotal PTX as an appropriate procedure in patients subsidiary of renal transplantation because of the low risk for hypocalcaemia.

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