■ CLINICAL RESEARH

Surgical Treatment of Refractory Hyperparathyroidism and Usefulness of the Intraoperative PTH

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Objective: To share our experience in the surgery of so-called refractory hyperparathyroidism (secondary and tertiary without response to therapy with calcitriol).
Material and methods: Retrospective study based on 41 patients–5 with secondary and 6 with tertiary hyperparathyroidism–referred by nephrology for surgical evaluation of their illness because of poor response to the medical treatment given.
Results: In 18 of the 41 cases we used the fast or turbo intraoperative PTH with reduction of more than 60 % in all patients. In the group in whom normal PTH was performed, we registered 2 secondary hyperparathyroidisms with no significant decrease and persistence of symptoms. One of them was reoperated successfully.
Discussion: Subtotal or total parathyroidectomy with reimplant represents the treatment of choice in refractory hyperparathyroidism with good results in most of the series reviewed.

Key words: Refractory hyperparathyroidism. Secondary hyperparathyroidism. Tertiary. PTH. Subtotal or total parathyroidectomy.

Tratamiento quirúrgico del hiperparatiroidismo refractario y utilidad de la paratirina intraoperatoria
Objetivo: Dar a conocer nuestra experiencia en la cirugía del denominado hiperparatiroidismo refractario (secundario y terciario sin respuesta al tratamiento con calcitriol).
Material y métodos: Estudio retrospectivo con revisión de 41 pacientes (35 con hiperparatiroidismos secundarios y 6 terciarios) remitidos por nefrología para valoración quirúrgica de su enfermedad ante la mala respuesta al tratamiento médico.
Resultados: En 18 de los 41 casos se utilizó la determinación de paratirina rápida o turbo intraoperatoria, con descenso superior al 60 % en todos los pacientes. En el grupo en que se empleó paratirina normal registramos 2 hiperparatiroidismos secundarios en los que la citada hormona no descendió significativamente y los síntomas persistieron, uno de los cuales fue reintervenido con éxito.
Conclusiones: La paratiroidectomía subtotal o total con autotrasplante es el tratamiento de elección en el hiperparatiroidismo refractario, con buenos resultados en la mayoría de las series consultadas.

Palabras clave: Hiperparatiroidismo refractario. Hiperparatiroidismo secundario. Terciario. PTH. Paratiroidectomía subtotal o total.

INTRODUCTION

In patients with chronic, end-stage renal failure (ESRF), one of the most important problems nephrologists face is controlling the hypersecretion of parathyrin (PTH) due to hyperplasia of the parathyroid glands. Orally or parentally administered calcitriol is generally used in an attempt to curb this hypersecretion; cases of secondary or tertiary hyperparathyroidism failing to respond to this medical alternative are considered to be refractory.

In hyperparathyroidism secondary to ESKF there is a tendency to develop hypocalcemia and intact PTH values are generally higher than in the primary forms of the disease; figures of 150 pg/mL or higher (and not below this level even when they are above the 60 pg/mL upper threshold of normality for serum PTH) are indicative of the illness. It is relatively easy to find serum levels in excess of 1000 pg/mL, since calcium, vitamin D, and phosphorus are contributing factors in originating it. Tertiary forms of hyperparathyroidism are states in which there is autonomous hyperproduction by the gland, usually occurring in patients diagnosed as having secondary hyperparathyroidism with poor functional response following kidney transplant.

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When medical treatment fails, surgical sub-total or total parathyroidectomy is the treatment of choice, with good results, such as we have seen in our case series and we will go on to show in other published works consulted, albeit not without complications or the possibility of recurrence. Rapid or turbo PTH determination enables us to know in the operating theatre if there has been a significant decrease in PTH concentration, which is predictive of surgical success.

MATERIAL AND METHOD

Retrospective study covering the period between April 1990 and July 2004, based on the clinical histories of 41 patients diagnosed with secondary or tertiary hyperparathyroidism (HPT), referred by the Nephrology Department for surgical evaluation of their illness following a poor response, if any, to medical treatment with calcitriol (refractory HPT).

The clinical manifestations of the patients, who for the most part were on haemodialysis at the time of referral to otorhinolaringology, included: osteoarticular manifestations, psychiatric symptoms, high blood pressure, GI illness, and kidney stones. In addition to a full pre-operative blood work-up, we generally order complementary imaging studies, including ultrasound and gammagraphy of the thyroid if not already included in their medical file. At present, gammagraphy is generally performed with technetium-99-sestamibi or MIBI instead of thalium-201.

Since 2000, our hospital has used the rapid or turbo PTH test, which makes it possible to know if PTH levels have decreased significantly or not while the patient is still on the operating table. In this regard, we consider a reduction of more than 60% of the initial or pre-operative value to be significant, although the resulting post-operative PTH level should also be analyzed. We have used the intra-operative PTH value in 18 (43.9%) of the 41 patients.

The surgical techniques performed in order of frequency were sub-total parathyroidectomies, total parathyroidectomies with auto-transplant or adenoma resections. All surgical specimens were sent for pathology study and histological confirmation. The post-operative complications were classified as: *a)* temporary or permanent hypocalcemia (if corrected calcium figures of <8 mg/dL persist after 2 months), *b)* recurrent paralysis, *c)* haemorrhage, *d)* serohaematomas, and *e)* infection of the surgical wounds.

We have used Filemaker 5.5, Microsoft Access 2000 and Sigma databases. The Microsoft programme Excel was used for calculations, information management, tables, and charts.

RESULTS

Of the 41 patients, 19 were male and 22 female, with ages of 21 to 72 years (mean, 51 years); 35 had a diagnosis of secondary hyperparathyroidism and 6, tertiary hyperparathyroidism, which represent 29.5% of all HPT cases referred for surgery versus 70.5% of primary HPT in our case series over a period of 14 years.

More than 95% of the cases were included in the haemodialysis programme (dialysis three times per week); osteoarticular manifestations were the most common (in 21 patients; 51.2%) and consisted of generalized bone pain, polyarthralgia, and radiologically evident lytic bone lesions. In order of frequency, we found high blood pressure (14 patients; 34.1%), pruritus (21.9%), gastroduodenal involvement (17%), generally ulcus type or dyspepsia, nephrolithiasis (14.6%), and psychiatric manifestations (7.3%) in the form of anxiety, lability, depression, or memory loss.

Thyroid ultrasound and gammagraphy were performed in 31 patients, with sensitivity values of 59 and 78%, respectively. Plasma calcium determinations ranged from 10.8 to 12.9 mg/dL, with a mean value of 11.2 mg/dL. Previous normal PTH values varied between 119 and 1939 (mean, 824) pg/mL, whereas the intra-operative rapid PTH test results were somewhat lower (786 pg/mL; range, 100 and 2500 pg/mL). Table I presents the intra-operative, pre-operative, and post-operative PTH values in the 18 cases recorded (17 secondary HPT and 1 tertiary HPT), as well as the percentage decrease in each one. Note that, despite a decrease of >60% (significant) in all patients, two of the rapid post-operative PTH values remained clearly or pathologically elevated (320 and 700 pg/ml).

Insofar as the type of surgery is concerned, 36 sub-total parathyroidectomies (88%) were performed with 3 glands resected and part of a fourth hyperplastic one, leaving a well-vascularized piece the size of a normal gland. In the remaining surgeries, 2 resections of apparent adenomas and 2 total parathyroidectomies with auto-transplant from the forearm or sternocleidomastoid muscle were effected. In one case of secondary HPT, exploratory neck surgery was performed that failed to reveal enlarged or diseased glands. In 4 situations, total thyroidectomy (1) and hemithyroidectomies (3) were required due to an associated thyroid condition (multinodular goitre).

The pathology study confirmed hyperplasia of the parathyroid in 37 samples sent, although in another 3, the pathologist diagnosed the samples sent as adenomas (Table II). Among the post-surgical complications, we report 11 temporary hypocalcemias and 2 permanent hypocalcemias, which all told account for 31.7%. In this study we report not a single case of paraesthesia or recurrent paralysis that can be attributed to the surgery after exposing 81 nerves. We had 2 cases of post-operative bleeding in the first 48 h that required revision with general anaesthesia and haemostasis by means of ligature or bipolar clamp. The serohaematomas of the surgical wound (a total of 3) gradually remitted with conservative treatment and there were no cases of infection of the surgical wound.

More than 92% of patients had significant or very significant improvement in symptoms during their first year following surgery, with an especially significant decrease in bone pain and polyarthralgias. All would continue to undergo subsequent check-up with nephrology. Where surgery drew a blank in our series, ie when after meticulous cervical revision we were unable to find abnormal parathyroid glands, this was considered a failure, as were the 2 patients in whom the post-operative rapid PTH test

revealed persistent, abnormally high levels. One of them (pre-op PTH, 2500; post-op PTH, 700 pg/mL) corresponded to a secondary HPT mistakenly diagnosed as primary HPT in which what was thought to be an adenoma was removed (pathology result: hyperplasia). This patient underwent subsequent surgery in order to remove the other 3 hyperplastic glands; intra-operative PTH levels were determined again and returned to normal following resection in the second surgery, with good clinical outcome. The other male patient (pre-op/post-op, 1732/320 pg/mL) is awaiting further surgery and his initial clinical symptoms have not improved.

DISCUSSION

Several authors have analyzed parathyroid function (PTH-Ca curve) in patients receiving haemodialysis with PTH values greater than 150 pg/mL.[1-3] Rodríguez et al[1,2] conducted several studies of this type comparing PTH reduction after 3 months of treatment with intravenous calcitriol and found that the higher the baseline PTH figure, particularly >1200 pg/mL, the lower the probability of response to medical treatment, as when the serum phosphorus levels exceeded 6 mg/dL. The classical indications of refractory HPT (secondary and tertiary) are intense HPT with figures of intact PTH >1000 pg/mL resistant to calcitriol in the presence of hypercalcemia and osteoarticular or muscular symptoms for which no other cause could be found.[4,5] Moreover, when gland volume and weight, estimated on the basis of imaging studies, exceeded 1 mL or 500 mg, resistance to medical treatment can be assumed, which must confirmed in all cases, and the eventual need for surgery.[6,7]

Although the ultrasound and gammagraphy were not terribly sensitive in most of the series, we believe that there is no conclusive reason for not ordering them, since they oftentimes provide us with information about associated thyroid disease and ectopic glands.[8] However, during the surgery itself, the surgeon's expertise and theoretical and practical knowledge regarding anatomy and cervical embryology are essential. Unlike primary HPT, bilateral examination of the 4 hyperplastic glands must be performed in the secondary and tertiary forms, bearing in mind possible atypical locations and the possibility of supernumerary parathyroid glands.[9] Systematic testing such as computerized tomography or magnetic resonance of the neck are not indicated.

The surgical procedure we used in most cases was subtotal parathyroidectomy. This technique is effective and capable of improving clinical symptoms and quality of life in patients with refractory HPT, as is total parathyroidectomy with auto-transplant.[10-12] However, both techniques can be accompanied by complications such as the possibility of permanent HPT, recurrent paralysis and persistence or recurrence of HPT.[13,14] This last complication has been estimated to occur in the short or medium term in between 5% and 15% of the cases depending on the series consulted, although there are few longer term studies (5 years or more) in which the percentage of recurrences would probably be higher.[15,16] Incomplete or insufficient resection of the hyperplastic tissue, undetected ectopic glands, supernumerary parathyroid glands, and parathyromatosis, multiple, small, nodular lesions of hypercellular parathyroid tissue distributed throughout the soft tissues of the neck are a well-known cause of recurrence of the disease.[16,17] In cases where general anaesthesia is absolutely contraindicated, percutaneous injection of ethanol into the gland has been described by means of ultrasound guided fine needle punction, albeit the results published are not consistent.[18, 19]

The intra-operative rapid determination of PTH enables us to know and predict the success of surgery with a safety margin of between 95% and 100%.[20-22] Most studies consider reductions of more than 50%-60% to be significant. We would like to point out that this fact should be accompanied by normal or near-normal PTH levels that, as we indicated in the introduction, are almost always higher in primary

Table I. Rapid parathyrin test levels before (pre-op PTH) and after surgery (post-op PTH), with the respective percentage of decrease

Pre-op PTH	*Post-op PTH*	*Decrease, %*
1638	45	97.2
270	61	95.2
1087	94	91.3
520	45.6	91.2
100	6.3	93.7
81.1	Undetectable	100
1087	94	91.4
1696	96.2	94.3
250	90	64
177	89	95
242	Undetectable	100
930	26	98
1329	28	98
228	8.6	97
639	29	96
104	12	88.4
2500	700	72
1732	320	81.5

Table II. Pathology diagnosis according to the type of hyperparathyroidism (HPT)

Type of HPT by Pathology Analysis	*Hyperplasia*	*Adenoma*
Secondary	32	2
Tertiary	5	1

HPT. In 2 of the patients, post-operative PTH values were 320 and 700 pg/mL despite decreases of 81.5% and 72%, respectively, with persistence of initial symptoms. This corroborates the previous comment; we must insist and patiently carry out an exhaustive examination of all the diseased parathyroid glands, including possible locations such as the thymus, carotid sheath, retro-oesophageal space or upper mediastinum, which is not always easy to do. Nevertheless, our success rate is currently estimated to be 92.68%, including the satisfactory revision surgery of one of the patients, a figure that is similar to that published in other studies.[4,6]

CONCLUSIONS

The best treatment for secondary and tertiary HPT that are refractory to treatment with calcitriol is currently surgery for sub-total or total parathyroidectomy with auto-transplant.

Although surgery is not without complications, our outcomes (success in more than 92% of cases) and those in most series, are satisfactory, with verifiable clinical improvement with respect to osteoarticular manifestations.

The rapid or turbo determination of PTH levels provides us with intra-operative information as to whether or not there has been a significant decrease in concentration and enable us to be reasonably sure of not having left behind any hyperfunctioning, ectopic, or supernumerary parathyroid tissue.

The most common cause of failure following surgery is incomplete resection of the hyperplasia. Despite proper treatment, recurrences can occur, generally in the medium and long term.

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