

Surgical Management of Secondary Hyperparathyroidism in Patients with End-Stage Renal Disease: Surgical Approaches and Report of Cases

*Son Dönem Böbrek Hastalarında Gelişen Sekonder Hiperparatiroidizmin Cerrahi Tedavisi:
Cerrahi Yaklaşımlar ve Olgu Sunumları*

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Objectives: End-stage renal disease is a worldwide public health problem. While the survival time of the patients extends, additional pathologies such as secondary hyperparathyroidism occurs. The aim of the study is to review the surgical approaches to secondary hyperparathyroidism and present our experiences.

Patients and Methods: This retrospective study included five male patients (mean age 38.6 years) who were operated on for chronic renal failure between 2004 and 2008. The data of patients were collected from hospital records.

Results: The mean duration of hemodialysis was 106.8 months. All patients had ultrasonography and scintigraphy preoperatively. The mean value of preoperative and post-operative serum PTH was 2097 ng/ml and 36.5 ng/dl, Ca 11.48 mg/dl and 6.2 mg/dl, P 7.5 mg/dl and 4.4 mg/dl, ALP 527 IU/L and 89 IU/L. Total parathyroidectomy and sternocleidomastoid muscle autotransplantation was performed in all patients and one patient had right thyroidectomy in addition. Postoperatively, all patients received oral calcium carbonate and calcitriol. No serious postoperative complications occurred in any of these cases. The duration of hospitalization was 4.6 days on the average. Serum PTH was kept constantly below 300 ng/L in all cases in follow-up and no recurrent hyperparathyroidism was detected.

Conclusion: Although there are many types of surgery techniques in treatment of secondary hyperparathyroidism, total parathyroidectomy with autografting is the most accepted procedure with low recurrent and complication rate in end-stage renal disease patients.

Key words: Secondary hyperparathyroidism; end-stage renal disease; parathyroidectomy.

Amaç: Son dönem böbrek hastalığı dünya çapında bir sağlık problemdir. Bu hastaların yaşam süreleri uzadıkça sekonder hiperparatiroidizm gibi ek patolojiler de gelişmektedir. Bu çalışmanın amacı sekonder hiperparatiroidizme cerrahi yaklaşımları gözden geçirmek ve kendi tecrübelerimizi sunmaktadır.

Hastalar ve Yöntemler: Bu retrospektif çalışmaya 2004 ve 2008 yılları arasında kronik böbrek hastalığı tanısıyla ameliyat edilen beş erkek hasta (ort. yaşı 38.6) dahil edildi. Hasta bilgileri hastane kayıtlarından toplandı.

Bulgular: Hastaların ortalama hemodializ süresi 106.8 aydı. Bütün hastalar ameliyat öncesi dönemde ultrasonografi ve sintigrafi ile incelendi. Hastaların ameliyat öncesi ve sonrası dönemde ortalama serum PTH değeri 2097 ng/ml ve 36.5 ng/dl, Ca 11.48 mg/dl ve 6.2 mg/dl, P 7.5 mg/dl ve 4.4 mg/dl, ALP 527 IU/L ve 89 IU/L idi. Bütün hastalara total paratiyoidektomi ve sternokleidomastoid kasa ototransplantasyon yapılrken bir hastaya ek olarak sağ tiroidektomi yapıldı. Ameliyat sonrası dönemde tüm hastalar oral kalsiyum karbonat ve kalsitriol kullanılar. Hiçbir hastada ciddi komplikasyon görülmemiştir. Ortalama hastanede kalış süresi 4.6 gündür. Hastaların hepsi serum PTH düzeyleri 300 ng/dl altında seyretti ve hiçbir hastada takipler esnasında nüks hiperparatiroidizm görülmemiştir.

Sonuç: Sekonder hiperparatiroidizmin cerrahi tedavisi için birçok yöntem olsa da total paratiyoidektomi ve ototransplantasyon düşük nüks ve komplikasyon oranları ile son dönem böbrek hastalarında gelişen sekonder hiperparatiroidizmin için en kabul edilen tedavi metotlarındandır.

Anahtar sözcükler: Sekonder hiperparatiroidizm; son dönem böbrek hastalığı; paratiyoidektomi.

End-stage renal disease (ESRD) is a worldwide public health problem. The therapeutic approach for ESRD includes renal transplantation and dialysis programs. There were nearly 25,000 patients requiring hemodialysis (HD) because of end-stage renal disease in Turkey and 500 of these patients have a chance for transplantation per year.^[1] By the development of new technologies, the survival time of the patients with ESRD is being obviously extended. This extended survival time brings about additional pathologies such as secondary hyperparathyroidism (sHPT).^[2] There is growing evidence that patients with ectopic calcifications, calciphylaxis, the presence of renal osteodystrophy (osteitis cystica, calciphylaxis, metastatic calcinosis), have higher risk of morbidity and mortality.^[3] Total parathyroidectomy (TPx) with autografting of parathyroid tissue is currently considered as standard surgical procedure for the treatment of severe sHPT in ESRD patients.^[3] The relationship between ESRD and hyperparathyroidism (HPT) was first recognized in 1930.^[4] Wells et al.^[5] first performed successful autografting parathyroid tissue in sHPT.^[6] Since then, many therapeutic strategies were developed and discussed for sHPT in ESRD. Herein, we reviewed the types of surgical approaches with advantages and disadvantages for sHPT in ESRD and our patients treated with surgical intervention.

PATIENTS AND METHODS

We performed a retrospective study of five male patients (mean age 38.6 years) with chronic renal failure, who underwent total parathyroidectomy and sternocleidomastoid muscle autografting for sHPT between 2004 and 2008. Data were analyzed retrospectively from patient files. All patients had hemodialysis three times per week and hemodialysis was performed the day before operation. Only one patient underwent continuous ambulatory peritoneal dialysis before hemodialysis for five years. All patients had routine preoperative tests including complete blood counts, serum electrolytes, urinalysis, chest x-ray, electrocardiogram, and coagulation screening. Indication for TPx included unequivocal evidence of sHPT consisting of high level of para-

thyroid hormone (PTH) ($>500 \text{ pg/mL}$), detection of enlarged parathyroid glands by ultrasonography (volume of the largest gland $>500 \text{ mm}^3$ or diameter $>1 \text{ cm}$), hypercalcaemia ($>10.2 \text{ mg/dL}$) and/or hyperphosphataemia ($>6.0 \text{ mg/dL}$). The localization of parathyroid glands was performed with ultrasonography (US) and scintigraphy (SC). Additional investigation of magnetic resonance was done in two cases. All patients were operated under supervision of a single surgeon. The operation was performed under general anesthesia. A frontal cervical transverse incision was made two finger-breadths above the sternal notch. Tissues from skin to muscles were dissected layer by layer until the thyroid gland was exposed. Then the middle thyroid veins were isolated and ligated, the thyroid gland was turned over medially. By the combination of pre-operative ultrasonography and intraoperative exploration, all of the parathyroid tissues were carefully discovered and removed. The resected tissues were kept in sterilized saline, and parts of the glands were taken for the immediate frozen section pathological examination. Upon completion of the cervical operation, the identified parathyroid gland was sliced into 15-20 pieces ($1-2 \text{ mm}^3$ in size). The sliced parathyroid glands were transplanted individually into the muscular bed of the patients' sternocleidomastoid muscle. Finally, the muscle fascia was sutured with absorbable suture. For prevention of postoperative tetany all patients received oral or intravenous calcium if indicated. Parathyroid hormone was measured postoperatively. Hemodialysis was resumed for every patient, 24 hours postoperatively.

RESULTS

The demographic data of patients were shown in Table 1. The mean duration of hemodialysis was 106.8 months. Five of the patients had US investigation and hyperplastic glands were detected in all cases. The mean value of the lesions was 24 mm in diameter with 5 mm smallest and 38 mm biggest in US investigation. Also Tc 99 MIBI scintigraphy was performed in all patients and no supernumerary gland was found. Magnetic resonance imaging was used

Table 1. The demographic data of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Male	Male	Male	Male	Male
Age	27	39	52	28	47
Dialysis period (month)	108	120	84	60	192
Hypertension	-	-	+	-	+
Nephrolithiasis	+	+	-	+	+
Dyspepsia	+	-	+	+	-
Muscle weakness	+	+	+	+	+
Bone pain	+	+	+	+	+
Bone fracture	+	-	-	-	-

for two patients. The mean value of the resected gland was 22 mm, with the biggest one 35 mm in diameter and 4 gr in weight. All glands were confirmed as parathyroid hyperplasia by pathological diagnosis. The postoperative serum values were tested at the third day of operation. The values of preoperative and postoperative serum calcium (Ca), phosphorus (P), parathyroid hormone (PTH), alkaline phosphates (ALP) concentrations are shown in Table 2. The mean value of preoperative and postoperative serum PTH was 2097 ng/ml and 36.5 ng/dl, Ca 11.48 mg/dl and 6.2 mg/dl, P 7.5 mg/dl and 4.4 mg/dl, ALP 527 IU/L and 89 IU/L. Four parathyroid glands were removed from each patient. No supernumerary glands were observed in any patient. Total parathyroidectomy and sternocleidomastoid muscle autotransplantation was performed in all patients and one patient had right thyroidectomy in addition. The serum calcium levels decreased in three patients and intravenous calcium supplementation was started. Postoperatively, all patients received oral cal-

cium carbonate and calcitriol. No serious intraoperative or postoperative complications, such as recurrent laryngeal nerve damage, wound infection, massive hemorrhage or persistent hypocalcaemia occurred in any of these cases. The duration of hospitalization was 4.6 days on the average. After operation, clinical symptoms were ameliorated; especially the bone pain and muscle weakness disappeared. Serum PTH was kept constantly below 300 ng/L in all cases in follow-up.

DISCUSSION

Secondary hyperparathyroidism is common in patients with chronic renal failure, affecting most of those who are receiving hemodialysis.^[7,8] It is one the most well-known complication that influences mortality and quality of life in chronic renal disease patients. 40% of ESRD patients die from cardiovascular disease and the mortality risk is increased 25% with PTH levels higher than 495 pg/ml and with phosphorus levels higher than 6.5 mg/dl.^[6] Renal failure is a pow-

Table 2. The peroperative and postoperative calcium, phosphorus, parathyroid hormone, and alkaline phosphates values of patients

	Ca n: 8.5-10.5 mg/dl		P n: 2.4-4.1 mg/dl		PTH n: 10-65 ng/ml		ALP n: 44-147 IU/L	
	pre	post	pre	post	pre	post	pre	post
Patient 1	13.6	4.8	8	4.7	3175	12	630	112
Patient 2	10.4	5.2	9.2	4.7	3068	25.7	906	132
Patient 3	11.5	7.3	6.8	3.5	1600	47.9	359	76
Patient 4	9	7.8	7.6	5.5	1563	59	416	51
Patient 5	12.9	6.1	5.9	3.7	1079	38	324	74

Ca: Calcium; P: Phosphorus; PTH: Parathyroid hormone; ALP: Alkaline phosphates.

erful stimulus for parathyroid cell proliferation. Nakai et al.^[9] reported that among patients in whom the duration of hemodialysis was more than 10 years, the frequency of parathyroidectomy was about 10%, and after 20 years of dialysis it was about 30%. In the current study, we had three patients who had hemodialysis approximately for 10 years. Pathogenesis of sHPT due to chronic kidney disease is well described. The most important reasons are hypocalcemia, hyperphosphatemia, and deficiency of active vitamin D. Phosphate retention acts directly on parathyroid cells which stimulates PTH secretion and proliferation of the parathyroid cells. Also, expression of vitamin D receptor and calcium sensing receptor in parathyroid cells is diminished in these patients.^[2,10-14] Exertions on medical management of sHPT in ESRD have concentrated on reducing the metabolic derangements. The main aim is controlling hyperphosphatemia and hypocalcemia. Conservative treatment includes low-phosphorous diet, phosphate-binding substances, oral calcium, and vitamin D or one of its metabolites. And other hopeful drug calcitriol has been shown to inhibit parathyroid hyperplasia, suppress PTH secretion, and increase calcium absorption but the response to this treatment reached 20 to 50% in patients with high levels of PTH (750-1250 mg/dl).^[6] New medicines, calcimimetics, act on Ca receptors of the parathyroid cells as calcium agonists and suppress PTH secretion remarkably without inducing hypercalcemia or hyperphosphatemia.^[3] Minimal invasive interventions such as ethanol injection has been advocated by some authors. They advised that selective percutaneous injection of ethanol till PTH level decreases to 200 pg/ml is sufficient.^[15] This treatment was not approved by majority because of high risk of complications such as laryngeal nerve palsy, the difficulty of a surgical exploration following failed ethanol ablation, and experience-based success.^[16] Despite medical treatment 5% of the patients undergo parathyroid operations. The indications for surgery are debated and accepted by majority of the endocrine surgeons. The Kidney Foundation of the USA proposed clinical prac-

tice guidelines for bone metabolism and disease in chronic kidney disease. In guideline 14, surgical indications, operative procedures, calcium replacement therapy after parathyroidectomy, and imaging diagnosis of abnormal parathyroid glands are described.^[2,17] High level of PTH (>500 pg/mL), hypercalcemia (>10.2 mg/dL), hyperphosphatemia (>6.0 mg/dL), detection of enlarged parathyroid glands by ultrasonography (volume of the largest gland >500 mm³), and refractory to medical treatment consist of high bone turnover, osteitis fibrosa on X-ray, progression of ectopic calcification, calciphylaxis, progression of bone loss, anemia resistant to erythropoietin are indications for parathyroidectomy.^[17] In the current report, four patients' Ca levels were higher than 10.2 mg/dl, four patients' P levels were higher than 6 mg/dl, all patients' PTH levels were higher than 500 pg/dl and three patients' parathyroid gland volumes on USG investigation were bigger than 500 mm³. Moreover, one patient had spontaneous bone fracture which is an indicator of high bone turnover. There are accepted three main types of surgical procedures and variations of these approaches. These are subtotal parathyroidectomy (sTPx), total parathyroidectomy (TPx), and total parathyroidectomy with autotransplantation (TPx + AT). Sanbury first described sTPx in 1958, and Ogg first performed TPx in 1967. Wells was the first surgeon who reported TPx + AT in 1975.^[2,5,6,18,19] For the past 50 years, surgeons have debated the optimal operative management for patients with sHPT in ESRD. Every procedure has its own disadvantages besides advantages. Subtotal parathyroidectomy was the first procedure which was used for sHPT in ESRD.^[18] For many years it has been accepted as a standard surgical operation. The procedure starts with the excision of all parathyroid glands except the smallest one together with bilateral removal of the thymus glands. The smallest gland was chosen and half volume of the gland which is 30-60 mg tissue left back with its blood supply.^[18] The main defect of this surgical procedure is that it is very difficult to recognize which gland is suitable for preservation by observation with the naked eye. This may cause recurrence of hyper-

parathyroidism.^[18,20-22] Once recurrence occurs, reoperation on the cervical area may have a high risk, because tissue adhesion may make it more difficult to find the recurrent gland and accidental injury of the recurrent laryngeal nerve may occur. This method is less frequently used today.^[2,6,16,18,20-22] Total parathyroidectomy and autotransplantation was first performed by Wells et al.^[5] and called as Wells' method. This procedure is similar with subtotal parathyroidectomy in tissue selection. After all excision stages the smallest gland was chosen and 20 parathyroid particles 1-2 mm in length in a weight of 60-80 mg tissue, which is the amount necessary to provide a normal calcium metabolism grafted into the forearm.^[2,5,6,8,16,20-22] Reoperation is relatively simple for recurrent hyperparathyroidism induced by the hyperfunction of autografted parathyroid tissue, because surgical access to the forearm is simple, it does not require general anesthesia, and there is no risk of major surgical complications such as laryngeal nerve injury. The disadvantages of Wells' method include forearm scarring, long operation time, difficulty in inserting parathyroid tissue into the forearm muscle, and imprecision and blind excision of parathyroid tissue if recurrence develops as a result of graft hyperfunctioning.^[2,6] We used this technique in non-renal disease patients. The other autografting area is sternocleidomastoid muscle which was described by Geis et al.^[23] in 1973. In the same way as in Wells method the resection and tissue selection has been performed. After the strap muscles were closed, a 0.7-1.0 cm pocket was developed parallel to sternocleidomastoid muscle fibers. After it was certain there was no bleeding in the muscle pocket, four to six pieces of parathyroid gland measuring 1-3 mm in size were placed between the muscle fibers. The estimated weight of the autograft tissue is between 60-80 mg. The muscle fibers anterior to the pocket containing the parathyroid tissue were then sutured closed with unabsorbable sutures and the cephalad and caudad portions of the autograft site marked with hemoclips for future reference in case further reduction of functioning parathyroid tissue became necessary. Care

was taken not to traumatize the area of the autograft during closure of the incision in an effort to avoid bleeding into the area causing impaired revascularization of the parathyroid tissue.^[23,24] Parathyroid tissue is transplanted into the sternocleidomastoid muscle rather than other sites because of easy accessibility, one operative site, less graft ischemia, a low incidence of infection, and a high success rate due to excellent blood supply.^[20-24] Another autotransplantation method described by Hidai et al.^[25] in which parathyroid tissue pieces are injected into the forearm muscle using a 14-gauge needle. This method has similar incidence of graft uptake, recurrence, and complications with other autotransplantation procedures.^[20-22,25,26] After all types of surgery, attention must be kept on patients' postoperative course. While the autographed parathyroid tissue begins to function in two to three weeks, patients may have severe hungry bone syndrome in this period. Calcium replacement therapy is indicated when serum calcium level decreases to below 8.0 mg/dL. It is a good marker that, if the alkaline phosphatase level is higher than 500 IU/L preoperatively, the incidence of hungry bone syndrome will raise postoperatively. Calcium and calcitriol supplementation starts according to patients clinical signs. Medical treatment after parathyroidectomy is important to prevent recurrent HPT and adynamic bone disease. Serum calcium, phosphorus and PTH levels must be under control. When the intact-PTH level is less than 100 pg/mL, the serum calcium level should be kept within 8-9 mg/dL, and when the intact-PTH level exceeds 100 pg/mL the serum calcium should be kept between 9 and 10 mg/dL.^[3] Subtotal or total parathyroidectomy with autotransplantation will lead to some problems which include persistent severe hyperparathyroidism, recurrent hyperparathyroidism, transplantation of parathyroid carcinoma into the graft area or malignant transformation of benign gland fragments, and permanent hypoparathyroidism. Many authors reported that the surgical treatment for secondary hyperparathyroidism in ESRD, both subtotal parathyroidectomy and total parathyroidectomy with autotrans-

plantation resulted in almost the same clinical improvement and recurrence rate.^[27-31] The incidence of persistent or recurrent sHPT varies between 4%-25%. Recurrent disease is related to the management of the underlying renal disease, in preventing hypocalcemia, the amount of residual functioning parathyroid tissue, and the duration of life. Tominaga^[2] who has the biggest series consisting of 1141 patients reported that persistent or recurrent sHPT was 4.0%, and 1.6% required reoperation. He mentioned that mediastinal parathyroid gland was the most common cause of persistent HPT and to avoid this manner Tc99 MIBI scintigraphy and US should be routinely carried out preoperatively. In all of our cases we perform US and scintigraphy in preoperative course and in the current study we did not detect any supernumerary gland and in follow-up we had no recurrent disease. In order to suppress parathyroid secretion completely and reduce recurrent hyperparathyroidism, total parathyroidectomy without autotransplantation was performed in 1967 by Ogg.^[19] Further clinical experience showed that this method was not useful, not only because lifelong substitution therapy was subsequently necessary, but also because osteopenia developed in the absence of PTH.^[2,6] In summary, total parathyroidectomy and autotransplantation is superior to the other techniques because the mass of parathyroid tissue is reduced without causing hypoparathyroidism. The grafted tissue secretes an adequate amount of parathyroid hormone resulting in normal serum calcium levels and remineralization of bone. Graft-dependent recurrent hyperparathyroidism is extremely rare. If recurrent hyperparathyroidism occurs, a part of the tissue can be removed easily under local anesthesia. The function of the grafted tissue can be followed in most patients by determination of the PTH concentration.

In conclusion, the total parathyroidectomy with autotransplantation is feasible, safe and effective for the patients with secondary hyperparathyroidism in end-stage renal disease patients, while its long-term effect will be further investigated after obtaining more samples and much longer follow-up.

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