

## Current status of parathyroidectomy for secondary hyperparathyroidism in Japan

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### Introduction

Hyperparathyroidism (HPT) is a common complication in haemodialysis patients, associated with morbidity and sometimes mortality [1]. In the majority of patients with secondary hyperparathyroidism (2HPT), this can be managed by medical treatment but this does not always give adequate control of the parathyroid disorder. Some patients require intervention treatment of the parathyroid glands including parathyroidectomy (PTx) and percutaneous ethanol injection therapy (PEIT). Successful surgical treatment achieves a dramatic drop of the parathyroid hormone (PTH) level, relieves the patient from clinical symptoms and reduces mortality [2].

Surgical indications in 2HPT and the frequency of PTx might be influenced by medical therapy, i.e. vitamin D and vitamin D analogues injection therapy, sevelamer hydrochloride, calcimimetics, etc., and the composition of the haemodialysis patients, i.e. race, gender, age and duration of haemodialysis. In this review the current status of PTx for 2HPT in our country is presented including the experiences from our department.

### Background and frequency of parathyroidectomy in Japan

There are many haemodialysis patients in Japan (2069.9 per million inhabitants in 2006) and the number of haemodialysis patients has gradually been increasing; at the end of 2006, it reached 264 000. We have very limited opportunities to perform kidney transplantation (~1000 patients/year), and in Japan our patients have to continue haemodial-

ysis for long term; ~25% continue haemodialysis for >10 years.

The Japanese Society for Dialysis Therapy (JSDT) reported that in Japan the frequency of PTx was ~10% in patients who had had haemodialysis for >10 years and ~30% among those being haemodialyzed for >20 years. At the end of 2004, in our country a total of 10 216 (5.9%) haemodialysis patients have undergone PTx. Between June 1973 and December 2007 a total of 2412 patients underwent PTx for 2HPT in our department, corresponding to ~20% of all PTxs for 2HPT in Japan. Because the registry of PTx for 2HPT is not generally available in Japan, the development of PTx in our country cannot be investigated with certainty. However, in our department the annual number of PTx has clearly been increasing, especially after the proposal of guidelines for treatment of 2HPT has been given by JSDT in 2004.

Recently, Dialysis Outcomes and Practice Pattern Study (DOPPS) evaluated the situation and quality of haemodialysis therapy in European countries, the United States of America (USA) and Japan from 1996 to 2001. The study presented the frequency of PTx in haemodialysis patients in each country. Compared with European countries, the frequency in Japan was less, both at baseline and during the course of the study (the prevalence was 4.1% and the incidence of PTx at follow-up was 0.6/100 patients-year) [3].

### Surgical indications for 2HPT

Initially the surgical indications for 2HPT were empathized by symptoms of 2HPT (bone and joint pain, muscle weakness, itching, irritability, etc.) and bone disease, osteitis fibrosa. After initiation of vitamin D and vitamin D analogues, the clinical findings of 2HPT have clearly changed. High serum phosphate (P), calcium (Ca) and PTH levels may be persisting without severe symptoms and high bone turnover. It has been clarified that among patients with chronic kidney disease (CKD), high values of P, Ca and PTH are associated with mortality mainly due to cardiovascular complications induced by ectopic calcification [1]. When serum P, Ca and PTH levels cannot be maintained within target ranges, medical treatment including active vitamin D therapy should not be continued and parathyroid

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intervention therapy should be considered to avoid progression of ectopic calcification. The JSDT guidelines proposed that parathyroid intervention therapy should be recommended in patients with severe HPT (persistent high serum level of the intact PTH level  $>500$  pg/mL), associated with hyperphosphataemia (serum P  $> 6.0$  mg/dL) and/or hypercalcaemia (serum Ca  $>10.0$  mg/dL) that are refractory to medical therapy. Moreover, in patients suffering from clinical symptoms, i.e. bone and joint pain, muscle weakness, irritability, itching, bone loss, anaemia resistant to erythropoietin, cardiomyopathy, calciphylaxis, etc., parathyroid intervention therapy should certainly be considered [4].

Assessment of parathyroid mass with ultrasonography (US) is an important factor in predicting the response of medical treatment and in deciding on surgical treatment [5]. In CKD patients, parathyroid glands initially grow diffusely and polyclonally and are then transformed into nodular hyperplasia with several nodules in which parathyroid cells proliferate monoclonally and with high growth potential [6]. Moreover, in parathyroid cells of within nodules, the expression of vitamin D receptors (VDR) and calcium-sensing receptors (CaSR) are diminished [7,8]. These findings indicate that 2HPT due to nodular hyperplasia may be resistant to medical treatment. The volume of parathyroid gland can be estimated by US, and a gland whose volume exceeds  $500 \text{ mm}^3$  or largest diameter is  $> 1 \text{ cm}$  has probably developed nodular hyperplasia [9].

The guidelines recommend surgical treatment at an early stage of 2HPT. In our series we evaluated the intact PTH level, alkaline phosphate (Al-P) and total glandular weight at PTx and compared the results of patients who underwent PTx during 1986–1990 (152 patients) and during 2001–2006 (899 patients). The mean values ( $\pm$ SD) of PTH decreased from  $1409.8 \pm 836.7$  pg/mL to  $1152.4 \pm 4837.7$  pg/mL, the Al-P level changed from  $748.5 \pm 647.4$  IU to  $466.6 \pm 387.2$  IU and the weight of glands removed at surgery decreased from  $3296.8 \pm 2047.1$  mg to  $2460.0 \pm 1895.4$  mg. Our findings clearly indicated that in our department PTx has gradually been performed at an earlier stage of the development of the parathyroid disorder.

## Surgical procedures

There are many variations in procedures to accomplish PTx, which include subtotal PTx, total PTx with autograft and total PTx without autograft [4,10]. Subtotal PTx and total PTx with autograft are widely accepted for 2HPT. There are no significant differences in the efficacy and recurrence rate between the two operative procedures [4,10]. However, according to our experience, subtotal PTx is frequently followed by recurrent HPT due to residual parathyroid tissue in the neck. When re-neck exploration is required there is a higher risk of injuring recurrent laryngeal nerves than that at the initial operation, and re-operation seems to imply some risk of parathyromatosis. Therefore, we changed our operative procedure early on, from subtotal PTx to total PTx with forearm autograft, and have continued this procedure for  $> 20$  years. For patients who require long-

term haemodialysis after PTx, the risk or recurrence is not negligible ( $\sim 20\%$  10 years after PTx) [4]. Because it is easier and safer to remove residual parathyroid tissue from the forearm at recurrence compared with a neck re-exploration, total PTx with forearm autograft is, in our opinion, recommended in a patient who has to continue haemodialysis for long periods after the operation. This procedure is nowadays chosen for 2HPT in 90% of all institutes in Japan.

Total PTx without autograft is not suitable for patients who will receive a kidney transplant, since the control of the serum Ca level may be difficult following kidney transplantation, and it has not been established whether hypoparathyroidism may be harmful in patients receiving long-term haemodialysis.

PEIT is widely accepted as a treatment for advanced 2HPT in Japan [11,12]. 2HPT can be managed in the long-term by PEIT provided that only one parathyroid gland is enlarged to  $>500 \text{ mm}^3$  as estimated by US [12]. At surgery after PEIT it is usually difficult to identify the parathyroid tissue and the recurrent laryngeal nerve. PEIT should therefore be limited to patients in whom only one gland is substantially enlarged and the PEIT procedure should be performed by skilled operators as well as an eventual subsequent PTx.

## Clinical improvement and survival rate

The effect of PTx is dramatic. Serum Ca and P can be easily controlled after PTx. Symptoms are quickly relieved by successful PTx. The bone mineral content in trabecular bone measured by X-ray absorptiometry increases by  $\sim 10\%$  after PTx. The bone biopsy has shown that bone resorption is immediately suppressed and bone formation is accelerated after PTx [13]. Recently it has been shown that patients who have suffered from DCM-like heart symptoms demonstrate marked improvement after PTx [14]. Unfortunately, vascular and valvular calcifications are not usually affected even by a successful PTx. It is therefore important that PTx should be performed at an early stage, before the calcification has become progressive.

We have evaluated survival rates after PTx in 2000 patients who underwent total PTx with forearm autograft in our department. Patient's survival after PTx for advanced 2HPT was extremely good in our experience. The overall 10-year survival rate after PTx was 77.6%, and 50% survival period was 189 months. Ten-year survival rate estimated from the beginning of haemodialysis was 99.0% and 50% survival period was 337 months.

In our series the mortality—defined as death within 1 month after PTx—was 3/2000 (0.15%). The frequency of husky voice due to palsy of the recurrent laryngeal nerve was  $< 1\%$ , and re-operations due to wound bleeding did not occur.

## Problems facing PTx

In the future, we face more serious problems in connection with surgery for 2HPT, as high-risk patients, i.e. patients

with high age and severe cardiovascular complications, are increasing.

It is well known that parathyroid glands are located in ectopic sites, e.g. in mediastinum, in thyroid gland, around bifurcation of the common carotid artery (undescended glands) [15]. The incidence of mediastinal glands in our series was ~1.3% and the most common location was the aorto-pulmonary window. Originally these glands were removed after sternotomy, but recently we have changed the technique and will now excise mediastinal glands by an endoscopic technique. However, the removal of mediastinal glands, especially those located in the aorto-pulmonary window, by endoscopic operation is an invasive procedure with attendant risk of complications.

When the serum PTH level is re-elevated after total PTx with forearm autograft, some possible origins of PTH over-secretion should be considered, i.e. the autograft or a residual gland in the neck or mediastinum [4]. Although image diagnostic examinations are used, the origin can sometimes not be detected.

We sometimes encounter patients who suffer from unilateral palsy of the recurrent laryngeal nerve after initial PTx or PEIT and who are referred to our department for re-neck exploration because of recurrent/persistent HPT [4]. In these cases, the operations are very stressful because bilateral palsy of the nerve may develop stenosis of the laryngeal space and tracheotomy should be required.

Parathyromatosis is defined as multiple foci of benign functioning parathyroid tissue in the neck or mediastinum, and it is usually induced by rupture of the capsule of parathyroid glands during surgical exploration or PEIT. It is usually very difficult to diagnose parathyromatosis by image techniques, but if such complication is encountered during re-exploration for HPT, all grossly diseased tissue should be removed along with the surrounding tissues. Although the operation seems radical, there is a high risk that the exploration will be incomplete [16].

Parathyroid carcinoma is very rarely a pathological feature in HPT, especially in 2HPT due to CKD [17,18]. In our series only five haemodialysis patients with distant metastasis of parathyroid carcinoma were encountered. Two patients died of uncontrollable hypercalcaemia and in one patient the cause of death was calciphylaxis. The prognosis of parathyroid carcinoma is poor and radical excision by a surgical procedure is very difficult.

### Parathyroidectomy for secondary hyperparathyroidism in the calcimimetic era

Cinacalcet HCl is a new medicine that is an allosteric modulator of CaSR; it reduces the PTH-secretion by binding to CaSR in the parathyroid cells. This medicine has been available all over the world including Japan and should have an impact on the treatment of 2HPT. PTx can dramatically control advanced 2HPT in most cases and improve quality of life and mortality of these patients. Based on clinical and economic aspects, PTx is a more suitable treatment for haemodialysis patients with advanced 2HPT, especially for patients who may require long-term haemodialysis.

However, many surgeons hesitate to perform operations on patients who belong to high-risk groups and on patients who might develop severe complications, i.e. bilateral recurrent laryngeal nerve palsy. Removal of mediastinal parathyroid glands is usually invasive; therefore, initially Cinacalcet HCl should be tried. When the patients cannot tolerate the medication, or PTH suppression is not sufficient, PTx should be considered.

Cinacalcet HCl may be indicated for patients who suffer from parathyroid carcinoma and parathyromatosis [19]. In the USA and European countries, Cinacalcet HCl is available for patients with uncontrollable hypercalcaemia due to parathyroid carcinoma [20].

After the induction of Cinacalcet HCl, surgical treatment may also be required. Choosing surgery, it is very important to detect and remove all parathyroid glands including ectopic and/or supernumerary glands at the initial operation, and total PTx with forearm autograft may still be suitable for patients with advanced 2HPT.

*Conflict of interest statement.* None declared.

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