Selective percutaneous ethanol injection therapy (PEIT) of the parathyroid in chronic dialysis patients—the Japanese strategy

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Introduction

High turnover bone disease due to excess parathyroid hormone (PTH) is one of the central features of bone abnormality in chronic dialysis patients [1]. Management of this type of uraemic bone disease has been aimed at the correction of the stimuli of PTH secretion. Thus, phosphate binders, in addition to dietary phosphorus restriction and oral active vitamin D sterols, have been used in most of these patients [2]. Among routinely available therapeutic modalities, calcitriol pulse therapy is considered to be the most potent medical therapy [3]. Nevertheless, some patients are even refractory to this therapy. Such patients usually have one or more enlarged parathyroid glands [4], and could be managed only by surgical parathyroidectomy until recently [5]. In this brief review, we would like to present a new approach to such patients which is currently becoming popular in Japan.

Parathyroid hyperplasia: pathophysiology and clinical significance

Recent researches with surgically removed parathyroid glands have elucidated that parathyroid hyperplasia in uraemic patients develops initially from diffuse hyperplasia [6]. Some cells with more severe reduction of calcitriol receptor [7] and calcium-sensing receptor within diffuse hyperplasia then begin to proliferate more vigorously and monoclonally [8], and progress to nodule formation, finally to nodular hyperplasia. As can be seen, patients with nodular hyperplasia are usually more resistant to medical therapy including calcitriol pulse therapy than those with diffuse hyperplasia [6].

Thus, it is critical to distinguish between diffuse and nodular hyperplasia in the selection of the optimal therapeutic modalities. One useful index is the size of the gland. Careful clinical observations and pathological analyses suggest that most of the glands larger than 0.5 cm³, or 1 cm in diameter, exhibit usually nodular hyperplasia [4,5]. In addition, blood supply to the gland evaluated by colour Doppler imaging may be another useful index for the existence of nodular hyperplasia [9].

Accordingly, we recommend the routine evaluation of the size and the blood supply to parathyroid glands by ultrasonography before starting calcitriol pulse therapy (Figure 1). If there is no evidence of nodular hyperplasia, PTH secretion can be usually controlled by calcitriol pulse therapy without difficulty. By contrast, if one or more enlarged glands suggestive of nodular hyperplasia are found, it is unlikely that PTH secretion can be controlled in the long-term even by calcitriol pulse therapy.

How have such patients been treated in the past? They may have been treated by calcitriol pulse therapy. Often this failed to cause significant suppression of PTH, but often caused hypercalcaemia so that at the end of the day one was forced to consider surgical parathyroidectomy. We propose that one should not try to treat such patients using calcitriol pulse therapy for more than 3 months if there is no evidence of significant PTH suppression, because we are concerned about the high risk of ectopic calcification. In such patients, we propose that one should even skip calcitriol pulse therapy (Figure 1).

New vitamin D analogues [10], calcimicetics [11], or their combinations may be effective in such patients. Whether this approach proves to be successful will have to be examined in near future. Until such evidence is available, we have adopted and developed a new strategy for such patients, i.e. percutaneous ethanol injection therapy (PEIT).

PEIT was introduced by Italian pioneers in early 1980s [12], initially as an alternative to surgical parathyroidectomy. We have further developed this technique as an adjunct to medical therapy instead. To this end we established the technique of ‘selective PEIT of parathyroid’. This involves selective destruction of enlarged parathyroid glands with presumed nodular hyperplasia using ethanol injection. The remaining glands with presumed diffuse hyperplasia are then managed by medical therapy. Today with sufficient theoretical background, operator experience and technological expertise, we can apply this technique efficiently and safely.

According to the recent survey by the Japanese Working Group on PEIT of Parathyroid, more than 600 patients have been treated by PEIT in Japan by September, 1998. Based on the results of this survey...
Fig. 1. Flow chart for the indication of selective PEIT of parathyroid. Calcitriol pulse therapy can be skipped in patients with suspected nodular hyperplasia.

and based on pathophysiological consideration, we proposed a ‘tentative guideline of selective PEIT of parathyroid’. This was done to establish the indications for this therapy, to optimize its efficacy and to minimize the risk of ethanol injection. Because the tentative guideline was published in Japanese [13], we give a brief summary here.

Principles of selective PEIT of parathyroid in uraemic patients

First of all, it is mandatory for this therapy to be performed by a skillful operator who is an expert of the anatomy and imaging of the neck. An ultrasonographic machine with sufficiently high specifications must be used, i.e. an electronic linear scanner or a mechanical sector scanner (7.5 MHz or more) with high resolution (0.5 mm). In addition, we strongly recommend the routine use of colour Doppler imaging in order to confirm destruction of parathyroid tissue to guarantee efficacy and safety of PEIT [14] (Figure 2). Colour Doppler imaging is also very helpful to localize the exact site of additional ethanol injections and to recognize recurrence of local cell growth.

The criteria for selective PEIT include: (i) high PTH concentration (intact PTH >400 pg/ml) at physiological calcium concentration corrected for albumin concentration (< 10.5 mg/dl); (ii) evidence of high turnover bone disease by imaging study or by serum markers of bone turnover, or ideally by bone biopsy; (iii) confirmation of at least one critically enlarged parathyroid gland by ultrasonography, within the reach of the PEIT needle; (iv) resistance to medical therapy and (v) consent of the patient. In addition, aluminium bone should be excluded.

In such patients, all glands larger than 1 cm in diameter or 0.5 cm³ in calculated volume, are selectively destroyed by injection of 90% ethanol with 1% lidocaine under ultrasonographic control. For safety, the initial injection volume should not exceed 80% of the calculated volume of the gland. It is also mandatory to confirm that the tip of the needle is in the centre of the gland. Ethanol should be injected slowly to avoid leaks from the gland. As reported earlier, we have developed a special needle for PEIT with side holes for homogeneous distribution of ethanol and with modification of the tip for easy detection by ultrasonography [15].

Since we are able to detect residual blood supply with high accuracy, additional ethanol injection can be performed with a minimal amount of ethanol. The interval between initial and subsequent additional ethanol injections varies depending upon the protocol [15–17]. Serum PTH and residual blood supply should be checked no later than 1 month after the initial
ethanol injection. With such care and technical modifications, the risk of recurrent nerve palsy has become minimal [17]. Nevertheless, compensated unilateral recurrent nerve palsy should be ruled out before PEIT.

Careful follow-up of parathyroid function is more important than the ethanol injection itself. The patients are usually treated using calcitriol pulse therapy directly after initial PEIT. This is followed by oral treatment with active vitamin D once the PTH concentration has been suppressed. In addition to the monthly check of serum PTH levels, it is useful to survey for the recurrence of cell growth by colour flow mapping at several months' interval or when PTH concentration begins to increase again. Recurrence of cell growth within the destroyed gland can be treated with injection of a minimum amount of ethanol whenever it is recognized. Nevertheless, the criteria for initial PEIT (see above) should be applied when undestroyed glands become enlarged. If the PTH concentration does not decrease despite complete destruction of the target glands, the presence of undetected or ectopic gland(s) should be excluded using scintigraphy, CT or MRI [14] (Figure 1). This is the only pitfall of PEIT because we do not routinely check ectopic glands prior to PEIT, in contrast to the preoperative evaluation before surgical parathyroidectomy.

On the other hand, permanent hypoparathyroidism is an important side effect of surgical parathyroidectomy which may be a cause of adynamic bone disease as recently recognized [18]. As we have reported recently, selective PEIT in combination with appropriate medical therapy causes a minimal risk of relative hypoparathyroidism at best. By contrast, care should be taken in performing PEIT for patients of recurrent hyperparathyroidism with a previous history of subtotal parathyroidectomy [17].

Another controversial issue that has to be addressed is the relative indication for PEIT and surgical parathyroidectomy. Of course, high-risk patients for surgical parathyroidectomy are good candidates for PEIT. Although the technique permits to destroy as many glands as we like, long-term follow-up suggested that patients with more than three critically enlarged glands should be managed by surgical parathyroidectomy.

Future Directions

As can be seen, selective PEIT has become a new option for the treatment of patients with severe secondary hyperparathyroidism resistant to medical therapy. We plan to report the final version of the guidelines next year after sufficient verification and discussion. Moreover, this route permits selective delivery of drugs into the parathyroid gland. As already reported by several groups including ours [19], direct injection of calcitriol solution has been tested in uraemic patients and gene transfer to enlarged parathyroid glands has been tried in rats. Such techniques of intervention may in the future provide the option of pharmacological parathyroidectomy.

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References