New clinical guidelines for selective direct injection therapy of the parathyroid glands in chronic dialysis patients

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Abstract
In 2000, the Japanese Society for Parathyroid Intervention issued the ‘Guidelines for percutaneous ethanol injection therapy of the parathyroid glands in chronic dialysis patients’. Since then, the concept of ‘selective PEIT’ has been well accepted and the number of patients treated by this method in Japan has increased. Recently, it has been reported that the effect of PEIT differs depending on the degree of nodular hyperplasia. Several new drugs have become available since 2000, and active vitamin D and its analogue have also been used for direct injection into the parathyroids. We present the new ‘Guidelines for selective direct injection therapy of the parathyroid glands in chronic dialysis patients’, a revised version of the 2000 Guidelines. We believe that these new guidelines are useful for selecting direct injection therapy in patients with advanced secondary hyperparathyroidism.

Keywords: percutaneous ethanol injection therapy (PEIT); percutaneous vitamin D injection therapy (PDIT); secondary hyperparathyroidism; ultrasonography; nodular hyperplasia

Introduction
Previously, surgical parathyroidectomy (PTx) was the only therapeutic approach for patients with severe secondary hyperparathyroidism. Then, in the 1980s, an epoch-making new technique, percutaneous ethanol injection therapy (PEIT), was introduced in Europe [1,2]. Though some Japanese pioneers started using this method in the early 1990s [3], details of the indications, techniques and post-PEIT management were not widely known. The PEIT procedure at that time was mostly carried out in an ‘experience-based fashion’, with no official standard.

The accumulated clinical and basic data now clearly suggest that in dialysis patients with severe secondary hyperparathyroidism, at least one parathyroid gland develops nodular hyperplasia [4], in which the receptors for vitamin D and calcium are decreased in number [5,6]. Parathyroid glands with nodular hyperplasia are resistant to medical therapy [5,7,8], and the method of ‘selective PEIT’ has been adopted throughout Japan [9–12].

The concept of ‘selective PEIT’ is to destroy the glands with nodular hyperplasia and then to manage the remaining glands with diffuse hyperplasia [13]. This post-PEIT management is the key to maintaining optimal parathyroid function [14]. After carefully assessing all aspects of PEIT, we established the first practical Japanese guidelines for PEIT in 2000 [15] by modifying tentative guidelines that were published in 1999 [16]. These guidelines published in 2000 have been widely used to guide bedside practice. By 2004, more than 2000 patients had been treated by PEIT in Japan. The cost of the technique is now covered by the Japanese health insurance system approved by the Japanese Ministry of Health, Labour and Welfare.

Since the 2000 guidelines, several aspects of the management of secondary hyperparathyroidism have changed. In the early 2000s, more importance was attached to the control of the parathyroid hormone (PTH) level, and there was a close focus on the optimizing bone turnover. The Japanese Society for Dialysis Therapy recently issued their ‘Guidelines for the management of secondary hyperparathyroidism in chronic dialysis patients’ [17]. These guidelines strongly emphasize survival as the basis for determining target levels for clinical parameters. Injectable active vitamin D, calcitriol, the vitamin D analogue maxacalcitol and sevelamer hydrochloride became available after 2000 in Japan, and these agents have also been directly injected into enlarged parathyroid glands [18,19].

Considering all of these developments, we present ‘A new version of the clinical guidelines for selective direct injection therapy of the parathyroid glands in chronic dialysis patients’ (Table 1), which is a revised version of the guidelines published in 2000 [15]. We believe that these guidelines are useful not only for selecting those cases that are resistant to medical treatment, but also for choosing between PEIT and PTx as the suitable intervention. In fact, the earlier use of active vitamin D is highly recommended to prevent the parathyroid gland overgrowth [20].
New clinical guidelines for selective direct injection therapy of the parathyroid glands

Table 1. A new version of the clinical guidelines for selective direct injection therapy of the parathyroid glands in chronic dialysis patients

Percutaneous ethanol injection therapy (PEIT)

1. Therapy is indicated for those who meet all three of the following criteria:
   (i) Difficult cases for continuous treatment, despite of medical treatments, showing intact PTH ≥ 400 pg/ml\textsuperscript{a} or hyperphosphataemia and/or hypercalcaemia induced by treatment\textsuperscript{b}
   (ii) Enlarged parathyroid glands with suspected nodular hyperplasia\textsuperscript{c} on ultrasonography
   (iii) Patients who have given informed consent to undergo PEIT\textsuperscript{c}

Exclusion criteria
   (i) Enlarged parathyroid gland located where ultrasonographic-guided puncture is impossible
   (ii) Paralysis of the recurrent laryngeal nerve on the opposite side\textsuperscript{d}
   (iii) Operation in the neck region for thyroid carcinoma, etc. is scheduled

2. PEIT equipment and techniques
   (i) Equipment: an electronic linear or convex ultrasound scan system with a frequency ≥ 7.5 MHz and colour Doppler function
   (ii) Needles: ~22 g, visible under ultrasonographic guidance (special needles for PEIT are commercially available)
   (iii) Technique: advance the needle visually, using ultrasonographic guidance to check the location of the tip. Flush with a minimum amount (0.02–0.1 ml) of ethanol, confirm jet echo within the gland, and then inject the required amount of ethanol. Adjust the amount of ethanol for the initial injection to ≥80% of the estimated volume of the gland on ultrasonography. When an additional ethanol injection is needed, the minimum amount should be injected into sites where there is blood flow
   (iv) Complications: PEIT can cause pain, haematomas or paralysis of the recurrent laryngeal nerve, so it should be performed with care

3. Post-PEIT management
   (i) Following the procedure, administration of active vitamin D sterols and control of serum phosphorus and calcium concentration must be started. The target i-PTH value should be between 60 and 180 pg/ml in the long term (intact PTH = 1–84 PTH × 1.7)
   (ii) Indications for additional PEIT: if the PTH concentration measured 2–4 weeks after PEIT does not decrease to the target concentration, PEIT should be repeated at a site with blood flow
   (iii) Indications for further PEIT: if the PTH concentration increases again, ultrasonographic examination should be repeated. If increased blood flow is seen in PEIT-treated glands, additional ethanol injections should be planned even if criterion (i) for initial PEIT is not satisfied
   (iv) Consider discontinuing the PEIT procedure in a refractory case to avoid tissue adhesion due to the injected alcohol, a condition which may lead to difficulty in subsequent parathyroidectomy (PTx)
   (v) If the target gland has been completely destroyed and the PTH concentration is still elevated, diagnostic imaging for ectopic glands should be carried

Percutaneous vitamin D injection therapy (PDIT)

This procedure is administered at an ‘advanced medicine hospital’ approved by the Japanese Ministry of Health, Labour and Welfare. The drugs used for this purpose are calcitriol and maxacalcitol. The indications, techniques and post-injection management procedures are similar to those for PEIT. The therapy differs from PEIT in the following points:
   (i) Lower risk to the recurrent laryngeal nerves, but similar risk of tissue adhesion
   (ii) Repeated injections are generally needed. If the PTH concentration increases again, consider switching to PEIT or PTx to avoid the risks frequent injections

\textsuperscript{a}The value of 1–84 PTH is converted to i-PTH by the formula: \text{Intact PTH} = 1–84 \text{ PTH} \times 1.7.
\textsuperscript{b}PEIT can be considered in patients with concentrations of i-PTH < 400 pg/ml if hyperphosphataemia and/or hypercalcaemia is present.
\textsuperscript{c}Estimated volume (calculated by length × width × depth × π/6) > 0.5 cm\textsuperscript{3} or abundant blood flow inside the gland suggests nodular hyperplasia.
\textsuperscript{d}If two or more glands have progressed to nodular hyperplasia, PEIT will probably be ineffective in the long term.
\textsuperscript{e}An explanation of the importance of regular checkup, restricted diet and compliance after PEIT should be given to the patient before obtaining informed consent for the procedure.
\textsuperscript{f}Because the paralysis caused by ethanol results in diplegia of the recurrent laryngeal nerves, concurrent bilateral injection of ethanol should not be considered, even if there is no paralysis of either laryngeal nerve before PEIT.

Indications

An intact PTH level >400 pg/ml should be considered as only a rough guide. Since continued vitamin D therapy for patients with hyperphosphataemia and/or hypercalcaemia leads to progressive ectopic calcification, PEIT can be considered for such patients who have an intact PTH level of <400 pg/ml.

More than 80% of glands with an estimated volume >0.5 cm\textsuperscript{3} proceed to nodular hyperplasia [4]. Therefore, parathyroid gland volumetry is important for predicting the effectiveness of vitamin D therapy [20]. Koiva et al. [21] noted that superior results are obtained in patients with one nodular hyperplastic gland. This is one of the major revisions in the new guidelines. Thus, ‘three or more glands’, one of the criteria for refractory response in the former guideline, is now changed to ‘two or more glands’. In addition to the principal indications mentioned in the new guidelines, high-risk PTx patients may also be candidates for PEIT [22].

Techniques

As there are various technical differences in equipment and needles used and the number of persons involved in PEIT
procedures among facilities, there are no major revisions in the chapter on techniques in the new guidelines.

Post-PEIT management

The use of active vitamin D is mandatory to prevent the recurrence of hyperparathyroidism, since glands with diffuse hyperplasia, which are not injected, are usually responsive to vitamin D therapy.

Understanding the limits of PEIT is important. If the target parathyroid is surrounded with leaked ethanol, subsequent surgical detachment will be difficult due to tissue adhesion. The average number of treatment sessions is 2.9 in the good-responder group, with an average duration of 3.4 ± 2.5 months [21]. Similarly, if the PTH concentration does not decrease even after five sessions of PEIT, then such cases are considered PEIT refractory and PTx is indicated [22]. One should always be aware of the possible existence of ectopic or supernumerary parathyroid glands.

Percutaneous vitamin D injection therapy (PDIT)

A statement on injectable agents other than ethanol appears in the new guidelines for the first time. This technique originated in Japan [18,19], and clinical data are accumulating. The mechanism of PTH suppression is thought to differ from that of PEIT [23,24]. Further discussion will be needed.

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Conflict of interest statement. None declared.

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