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Indication and efficacy of PEIT in the management of secondary hyperparathyroidism

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Abstract

Control of secondary hyperparathyroidism (SHPT) using active vitamin D analogues becomes difficult in advanced SHPT, because the enlarged parathyroid glands (PTGs) are resistant to medical therapy. Percutaneous ethanol injection therapy (PEIT) has been widely used in Japan since the 1990s as a surgical intervention for advanced SHPT, by selectively destroying only the enlarged glands with nodular hyperplasia (i.e. >0.5 cm^3, measured by ultrasonography). If there is only one PTG with nodular hyperplasia, PEIT will be successful with a small number of injections, and it then becomes possible to maintain target levels of parathyroid hormone by treatment with active vitamin D analogues. Recent studies have demonstrated that in the advanced phase of SHPT, it is desirable to perform PEIT when it is restricted to patients with not more than one PTG larger than 0.5 cm^3 in terms of superior prognosis can be obtained including efficacy, low recurrence, and long-term remission period.

Keywords: long-term prognosis; parathyroid gland; percutaneous ethanol injection therapy; secondary hyperparathyroidism; vitamin D analogues

Introduction

A common complication in patients on long-term dialysis is secondary hyperparathyroidism (SHPT), which causes mineral bone disorder of chronic kidney disease (CKD-MBD). Active vitamin D analogues are widely used as standard medical therapy for SHPT, but it can be difficult to maintain serum calcium and phosphate levels within the normal range, and response to medical therapy declines as SHPT progresses [1,2]. In the advanced stage, the parathyroid glands (PTGs) exhibit nodular hyperplasia, there is a reduced therapeutic effect on the secretion of parathyroid hormone (PTH) and the patient is considered to be resistant to medical treatment. In such cases, surgical parathyroidectomy (PTx) is the conventional treatment choice and has been widely performed in Japan [3]. In the 1980s, percutaneous ethanol injection therapy (PEIT) under ultrasound guidance was developed in Italy for PTG tumours and because the glands are physically destroyed, PEIT is also considered to be an effective treatment for resistant SHPT.

In 1994, Kitaoka *et al*. reported on the use of PEIT for SHPT [4], and it has since been widely used in Japan as a new intervention. Standardized guidelines for indications, equipment and postoperative management were produced in 2003 [5], consolidating the place of PEIT as a tool for managing advanced SHPT in Japan.

Efficacy of PEIT

In the 1990s when PEIT was first introduced, some reports from Europe indicated that PTH levels were reduced by $>30\%$ in only $\sim$40–60% of cases [6–8], whereas in Japan the success rate was comparatively high. In Kitaoka *et al*'s 1994 report [4], serum intact PTH levels decreased from 727 pg/mL to <200 pg/mL in seven of nine patients who underwent PEIT, and in the remaining two patients levels were maintained within the target range by postoperative medical therapy (i.e. vitamin D analogues). Those good results were obtained because not only the target gland but also secondary and tertiary glands in size were treated, and because of improvements in equipment, such as the addition of three small holes in the side of the needle to improve ethanol infiltration. Furthermore, another paper from Japan [9] reported that the mean serum PTH levels were reduced to 226 pg/mL after one session of PEIT targeting all glands >5 mm in size on ultrasonography, and their ratio of PTH reduction was equal to that of the previous report. The results of the two Japanese reports indicate that if all hyperplastic glands are destroyed by PEIT, serum PTH levels can be reduced to the target range. However, as the number of interventions increases, incidences of injection-related complications also increase. Therefore, the Japanese guidelines also recommend target glands of PEIT as >0.5 cm^3 or >1 cm in size, but not all glands were detectable by ultrasonography. Moreover, other studies state that the efficacy of PEIT is decreased or is nullified when

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the preoperative PTH level is >1000 pg/mL and there is more than one gland >0.5 cm^3 on ultrasonography [10,11]. Therefore, various factors, such as the stage of SHPT and the number of enlarged PTG, influence the efficacy of PEIT.

Factors contributing to the efficacy of PEIT

Number of enlarged glands. As the PTGs become >0.5 cm^3, or 1 cm in diameter, they became resistant to medical therapy, so the presence of enlarged glands is a strong indicator of responsiveness to conventional treatment [12]. Furthermore, histological analysis of surgically removed glands has confirmed that >90% of glands heavier than 0.5 g have nodular hyperplasia [13], so for PEIT to be effective all glands >0.5 cm^3 have to be destroyed.

According to the Japanese guidelines for PEIT of the PTG, glands with nodular hyperplasia are selectively destroyed and glands with diffuse hyperplasia are then managed by medical therapy [5]. If there is only one enlarged gland, a single session of PEIT will usually be successful, but if there are more than two, it becomes difficult to destroy all target glands with certainty in one session of PEIT and the number of interventions increases.

In a study comparing the number of enlarged glands in haemodialysis patients with intact PTH levels <300 pg/mL after PEIT, the efficacy was 66.7% with one gland, but only 7.7% if there were more than two [14]. In another study [15], there was a negative correlation between the number of glands >0.5 cm^3 and the efficacy of PEIT, although there was no correlation between the total number of enlarged glands and the efficacy (Figure 1a,b). Nakamura also reported that the efficacy of PEIT diminishes as the number of hyperplastic glands increases [11]. These reports confirm that superior results will be obtained with PEIT when there is only one PTG that is >0.5 cm^3.

Serum PTH levels. A recent clinical study reported that the serum PTH level was not reduced in the case of advanced SHPT with preoperative intact PTH levels >1000 pg/mL, even though PEIT was performed as described in other reports [10]. The authors considered that the reason for treatment failure was that the subject of their study had advanced SHPT, in which most of the enlarged glands are resistant to medical therapy, so multiple injections over a prolonged period are required to achieve an effect. This is undesirable because of the increased incidence of the side effects of ethanol leakage, such as pain, haemorrhage and recurrent laryngeal nerve palsy. Moreover, adhesion of surrounding tissue is exacerbated with repeated PEIT and thus the therapeutic efficacy diminishes.

We have recently shown that the odds ratio for success versus failure by multivariate regression analysis is 0.29 for preoperative intact PTH levels >500 pg/mL compared with <500 pg/mL [15]. In Europe and the United States, calcimimetics have shown superior efficacy as medical treatment for SHPT resistant to conventional treatment, but as of the end of 2007 they are not available in Japan, so interventions such as PEIT and PTx are the choices for SHPT resistant to medical therapy. Particularly, PEIT is desirable, and still effective, in the early phase when the incidence of CKD-MBD is thought to be low. In other words, PEIT is indicated at the stage when the patient is resistant to medical therapy, with only one enlarged PTG, and the indication for PTx is more advanced SHPT, or more than two enlarged PTGs.

Good prognosis after PEIT

At the time PEIT was first introduced, it was considered that subsequent treatment with active vitamin D analogues strongly influenced long-term post-precedural prognosis. When PEIT is successful, serum Ca and P levels, as well as the PTH level, decrease immediately after PEIT [16], enabling a strong inhibition of the PTH level with medical therapy. However, if this becomes difficult after PEIT, then the remaining PTGs have advanced hyperplasia and, in such cases, serum Ca and P levels increase, promoting a recurrence of SHPT. One group has reported that it is possible to maintain a low PTH level for 1 year after PEIT, if it is performed correctly [9], and furthermore, they also reported that PTH was maintained at an adequate level for at least 3 years with a combination of after-treatment and additional PEIT [17]. In both reports, the PTH level was decreased to the target level by the first session of PEIT,

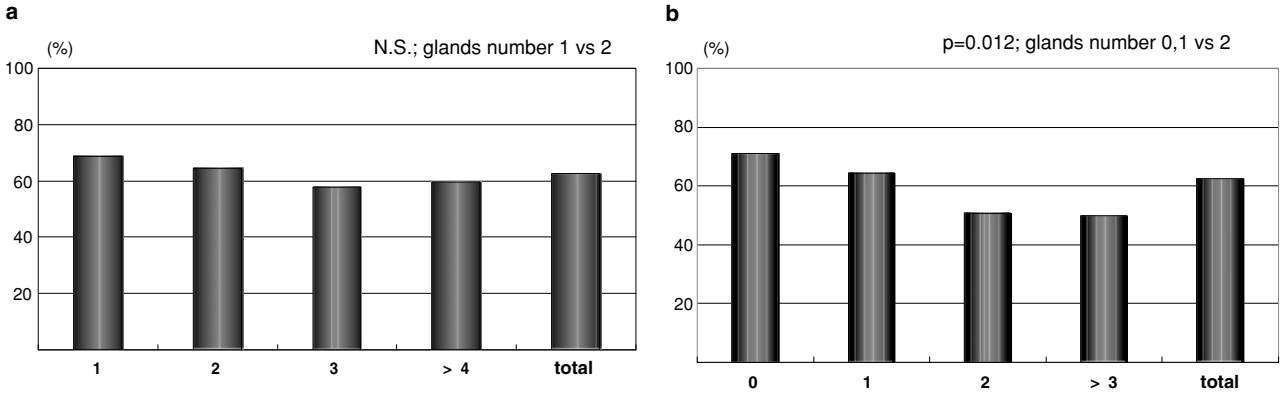

Fig. 1. Influence on the efficacy of percutaneous ethanol injection therapy (PEIT) of (**a**) the number of parathyroid glands and (**b**) the number of parathyroid glands with a volume ≥0.5 cm^3.

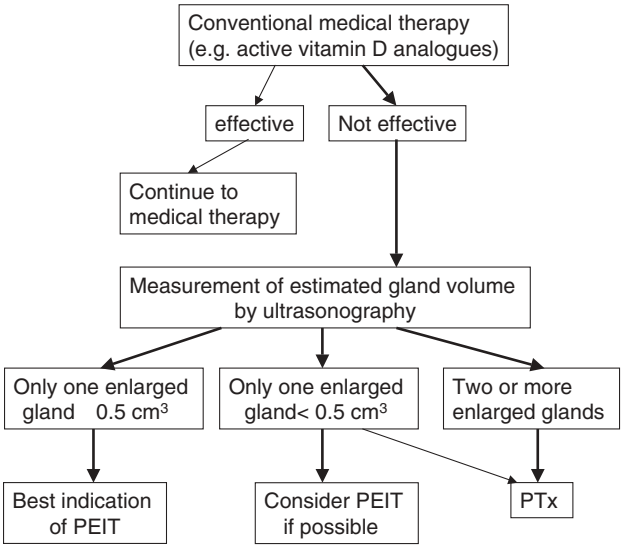

Fig. 2. Preferable indication of PEIT achieving good prognosis including high efficacy, low recurrence and long-term remission period. PEIT: percutaneous ethanol injection therapy, PTx: parathyroidectomy.

which suggests that the long-term prognosis is influenced by the rate of PTH decrease immediately after PEIT.

For PEIT to be considered an effective therapy for SHPT, serum PTH and Ca levels must be decreased to their target ranges by the first intervention, and then maintained in that range for a long period. However, the therapeutic effect of PEIT is greatly influenced by the skill of the operator, so a full assessment of outcomes is difficult in small-scale, single-centre studies, and instead requires large numbers of PEIT procedures performed in several centres under the same therapeutic guidelines to minimize the influence of variations in skill level between institutions. In addition, there were no standardized therapeutic guidelines for PEIT in the early 1990s, and therapeutic outcomes depend on correct indications, equipment, technique and postoperative management. Furthermore, improvements in mineral metabolism after PEIT have not been fully investigated.

In our study of a retrospective cohort of >300 subjects [15], based on the Japanese PEIT Guidelines [5], patients were divided into an effective group that achieved the specified levels of serum corrected Ca <10.5 mg/dL and serum intact PTH <250 pg/mL, and an ineffective group that failed to achieve these target levels after one session of PEIT. Active vitamin D analogues were used as after-treatment in all cases. In the effective group, the response period was defined as the period from the day on which target levels were reached until the day on which either target level was exceeded, and the remission period was defined as the period from the day on which target levels were reached until the day of repeat PEIT or PTx because of recurrent disease. PEIT was effective in 208 patients (66.2%), in whom serum intact PTH levels decreased from 603 ± 292 to 183 ± 62 pg/mL (ng/L), and serum corrected Ca levels from 10.7 ± 0.8 to 10.1 ± 0.5 mg/dL. The risk of relapse was evaluated by multivariate analysis using a logistic regression model, with the event of exceeding target levels (relapse) as a dependent variable. The odds of relapse versus non-relapse throughout the follow-up period was 2.37 in the presence of more than two hyperplastic glands versus one or no glands larger >0.5 cm^3. In addition, the event-free survival of the remission period was evaluated using Kaplan–Meier survival analysis and the remission period for the group with only one hyperplastic gland showed a significant extension by log-rank analysis. Nodular hyperplasia can be presented if PTGs are enlarged by between 0.25g and 0.5g [13]. In the case of only one enlarged gland <0.5 cm^3, this PTG may have nodular hyperplasia if it does not respond to medical therapy. In such a case, PEIT becomes an effective treatment if PEIT is possible technically [18]. Therefore, as shown in Figure 2, superior prognosis including high efficacy, low recurrence, and long-term remission period can be obtained with PEIT when there is only one enlarged gland >0.5 cm^3 or there is only one enlarged gland on which we can perform PEIT.

Conclusion

In Japan, where at present calcicimetics are unavailable, the presence of hyperplastic PTGs is a good indication for PEIT, even if the serum PTH level is <500 pg/mL. Superior results for PEIT, in terms of efficacy and superior prognosis, can be obtained when it is restricted to patients with not more than one PTG >0.5 cm^3.

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Conflict of interest statement. None declared.

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