

Percutaneous calcitriol injection therapy (PCIT) for secondary hyperparathyroidism: multicentre trial

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Abstract

A multicentre trial of percutaneous calcitriol injection therapy (PCIT) was designed to evaluate its clinical usefulness. During a 12-week period, measurement of intact PTH concentration, and other parameters, and ultrasonography were carried out in conjunction with PCIT in 19 haemodialysis patients with secondary hyperparathyroidism and enlarged parathyroid glands (PTGs) that were resistant to vitamin D pulse therapy. Calcijex was injected directly into the PTG three times per week on the patient's non-dialysis days: eight patients received a 2 µg/ml preparation (group A) and 12 received 1 µg/ml (group B). A strong clinical effect was observed in group A compared with group B, which suggests that the effect of calcitriol by direct injection is stronger when there is a higher concentration of calcitriol in the PTG. In group B, the cases with an initial intact PTH concentration <1000 pg/ml and a single enlarged PTG had a good response to the treatment. Concentrations of calcium and phosphate were not significantly changed in either group. All cases had decreased blood flow in the PTG after three episodes of PCIT and, although the size of the PTG was unchanged, or even a little increased, immediately after the treatment, it decreased gradually over 2–6 weeks. PCIT may be effective for comparatively slight secondary hyperparathyroidism, but further investigation is necessary because there were comparatively few cases.

Keywords: calcitriol; hyperparathyroidism; multicentre; percutaneous

in chronic dialysis patients [1], and management of this uraemic bone disease has been aimed at correcting the stimuli for PTH secretion. Thus, phosphate binders, in addition to dietary phosphorus restriction and active vitamin D sterols, have been used in most of these patients [2]. Of the routinely available therapeutic modalities, calcitriol pulse therapy is considered to be the most potent medical therapy [3], but some patients are refractory even to this. Such patients usually have one or more enlarged parathyroid glands (PTGs) [4] and require some interventional therapy, including surgical treatment. There are many choices of intervention, but direct injection of vitamin D into the PTG is one of the more attractive therapies for secondary hyperparathyroidism because of its few adverse events and its predictable effect [5,6].

However, in Japan, there is no medical insurance cover for percutaneous calcitriol injection therapy (PCIT), although the drug has been marketed for clinical use. It is strongly felt that there is an urgent need to clarify the clinical evaluation of the therapy, because it is the preferred modality from the view of the absence of recurrent nerve palsy compared with other parathyroid interventions. However, the procedure requires multiple injections and there is a possibility of lesser effectiveness of the treatment in the long-term management of secondary hyperparathyroidism.

We designed a protocol for clinical practice of PCIT as a multicentre trial and we evaluated its clinical usefulness.

Introduction

High turnover bone disease because of excess parathyroid hormone (PTH) is a major bone abnormality

Methods

Calcijex (1 and 2 µg/ml) was imported for the purpose of this research. Participation in the research by each institution was the permission of the IRB or ethics committee. Patients gave their written informed consent.

Measurement of the intact PTH (i-PTH) concentration and other parameters, and ultrasonography were carried out in conjunction with PCIT during a 12-week period. Patients received a direct injection of calcijex (1 and 2 µg/ml

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preparations) three times within a week on their non-dialysis days.

Statistical analysis was by Student *t*-test.

Subjects

Nineteen haemodialysis patients with secondary hyperparathyroidism and who were resistant to vitamin D pulse therapy with enlarged PTGs detected by ultrasonography (Table 1) underwent PCIT. The average duration of dialysis was 16.6 (13 ± 21) years and the average age was 57.4 (52 ± 73) years.

Eight cases received 2 µg/ml calcijex (group A) and 12 cases received 1 µg/ml (group B) by local direct injection. Group B was divided into three subgroups for further analysis (Table 2): B1 (*n* = 5) consisted of cases with i-PTH concentration < 1000 pg/ml and one enlarged PTG; B2 (*n* = 4)

Table 1. Criteria for parathyroid calcitriol direct injection (PCIT) for patients on maintenance dialysis because of chronic renal insufficiency

- Parathyroid calcitriol direct injection (PCIT) will be indicated in patients meeting all four conditions, in addition to their giving consent to undergo this therapeutic intervention.
1. Intact PTH ≥ 400 pg/ml
 2. Evidence of fibrous osteitis or highly relocated bone (e.g. imaging, bone metabolism marker).
 3. Resistance to medical therapies including oral or intravenous active vitamin D therapy.
 4. Ultrasonographic evidence of hypertrophic parathyroid gland. PCIT is contraindicated in the following cases:
 1. Hypertrophic parathyroid gland in a site where ultrasonographic paracentesis cannot be performed.
 2. Patients unable to remain immobile and in the correct position.
 3. Physician judges PCIT to be inappropriate.

Table 2. Three subgroups of group B

	Initial i-PTH concentration	No. of enlarged glands
B1 (<i>n</i> = 5)	< 1000	1
B2 (<i>n</i> = 4)	< 1000	> 2
B3 (<i>n</i> = 3)	≥ 1000	> 2

consisted of cases of i-PTH concentration < 1000 pg/ml and more than two enlarged PTGs; and B3 (*n* = 3) consisted of cases of i-PTH concentration > 1000 pg/ml and more than two enlarged PTGs.

Results

In group A, the direct injection of calcitriol decreased the i-PTH concentration from 662.5 ± 362.5 pg/ml (mean ± SD) to 169 ± 84 pg/ml (*P* < 0.002), a decline of 74.4% (Figure 1).

In group B, the direct injection of calcitriol decreased the i-PTH concentration from 937.5 ± 600.3 pg/ml (mean ± SD) to 568.3 ± 501 pg/ml (*P* < 0.002), a decline of 34.6% (Figure 2).

As for the three subgroups, the decrement in the concentration of i-PTH after treatment was from 704 ± 242 to 155 ± 155 pg/ml (*P* < 0.002) (group B1), from 574 ± 273 to 385 ± 185 pg/ml (*P* < 0.01) (group B2) and from 1810 ± 358 to 1336 ± 181 pg/ml (*P* < 0.05) (group B3), a decline of 78.0, 32.9 and 26.2%, respectively (Figures 3–5). Serum concentrations of calcium and phosphate were not significantly changed in any of the groups.

All cases revealed decreased blood flow in the PTG after three episodes of PCIT. The size of the parathyroid was unchanged or a little increased just after the treatment, but it decreased gradually after 2–6 weeks, and the vascularity was slightly decreased (Figure 6).

Discussion

A strong clinical effect of calcitriol was observed in group A (2 µg/ml) compared with group B (1 µg/ml), which suggests that the effect of calcitriol by direct injection is stronger when there is a higher concentration of calcitriol in the PTG.

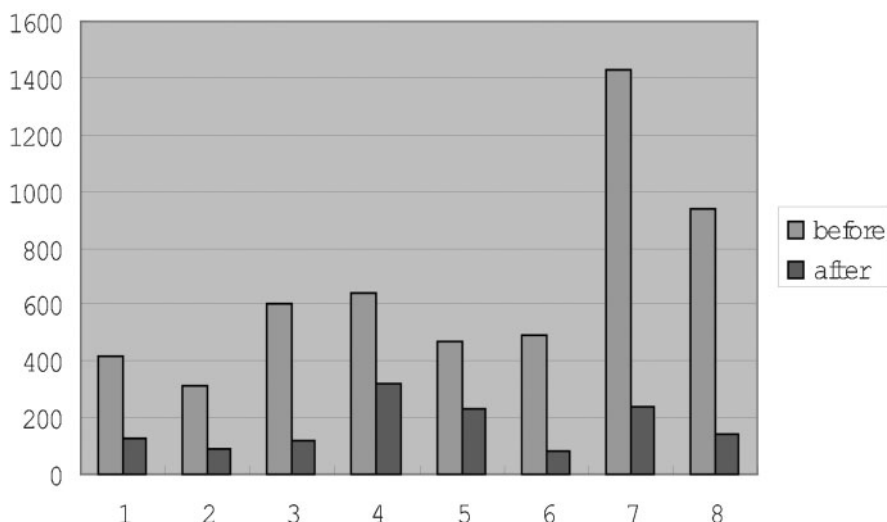


Fig. 1. Change in the i-PTH concentration after treatment in group A. Gray bars, before treatment; black bars, after treatment.

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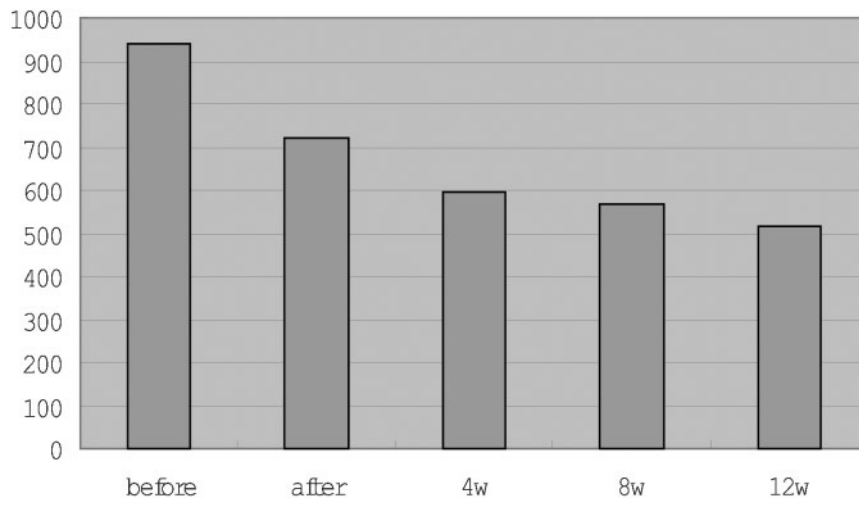


Fig. 2. Change in the i-PTH concentration after treatment in group B.

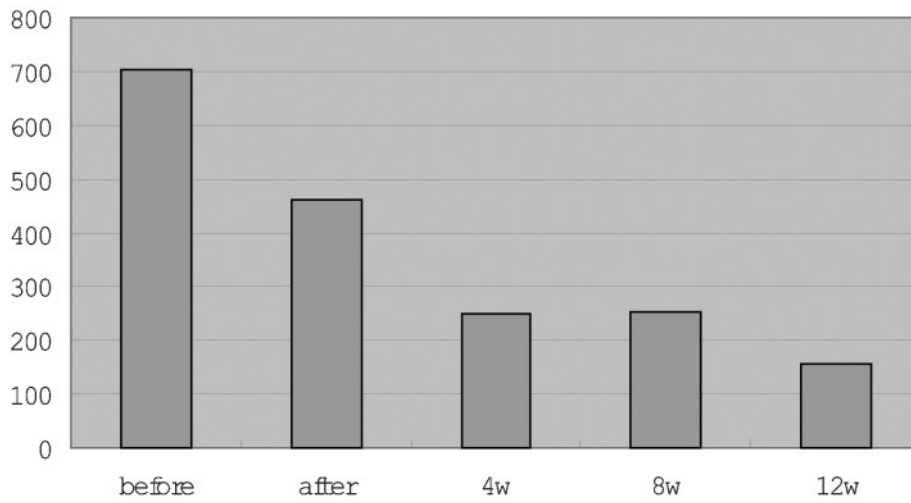


Fig. 3. Change in the i-PTH concentration after treatment in group B1.

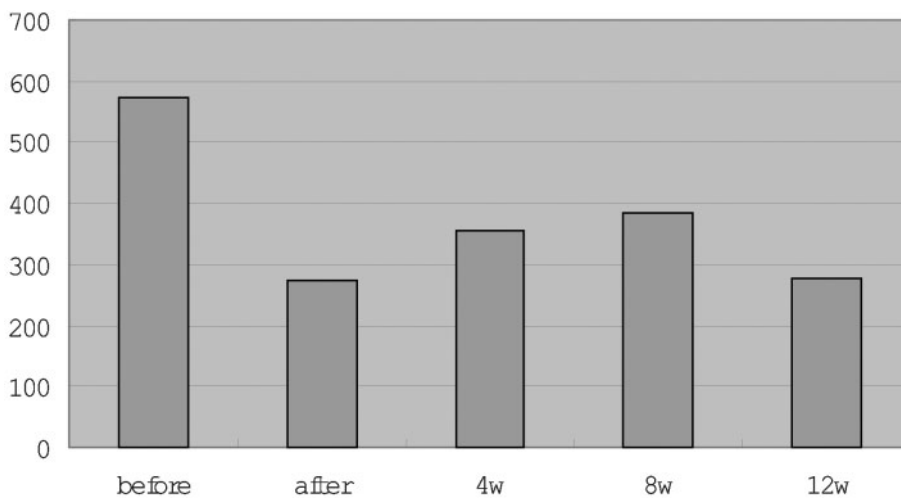


Fig. 4. Change in the i-PTH concentration after treatment in group B2.

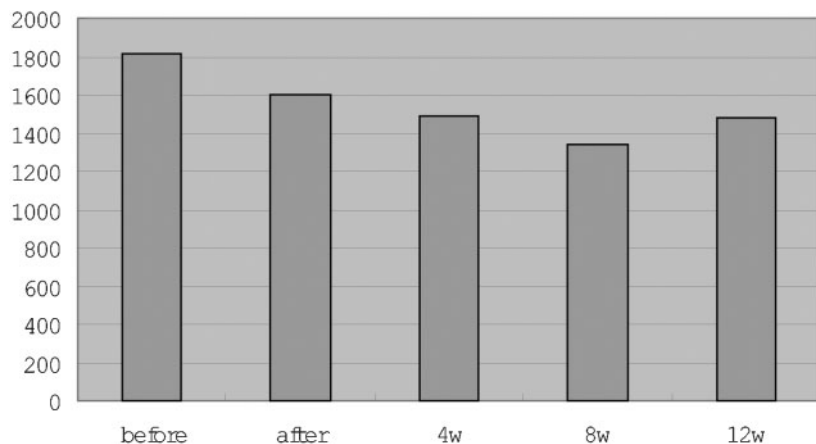


Fig. 5. Change in the i-PTH concentration after treatment in group B3.

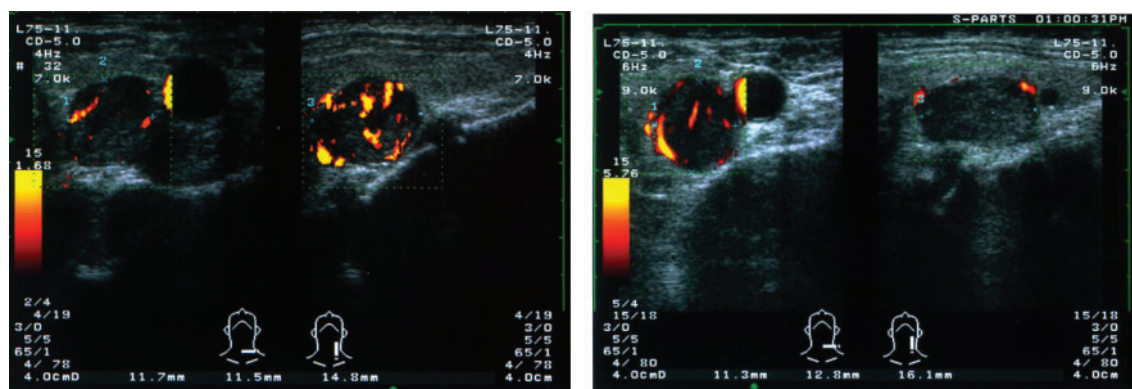


Fig. 6. Changes in the ultrasonographic images after direct injection of calcitriol.

In group B, the cases with an initial i-PTH concentration < 1000 pg/ml and a single enlarged parathyroid gland had a good response to this treatment. This result shows the possibility that PCIT is effective for comparatively moderate secondary hyperparathyroidism, but further examination is necessary because there were comparatively few cases.

We tried direct injection of calcitriol for the first time in the world in 1994 [5], but there was no acknowledgement of the therapy at that time. In the present study, we tried direct injection of calcitriol (1 µg/ml) three times per week for 2 weeks to determine the exact effect of this therapy. This protocol (six injections in total) induced a better clinical effect than single weekly injections (three in total).

No recurrent nerve palsy was observed throughout the present multicentre trial, which shows the possibility of safe implementation of this parathyroid intervention by many institutions.

PCIT has the advantage that the active vitamin D concentration in the blood does not increase and the serum calcium concentration is also not too high. We consider that PCIT has excellent clinical utility and expands the range of treatments for secondary hyperparathyroidism. However, there is a need for further

examination of the most effective concentrations, dosages, administration intervals, etc.

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