THE EFFECT OF PERCUTANEOUS ETHANOL INJECTION THERAPY IN TREATMENT OF HYPERPARATHYROIDISM IN CHRONIC DIALYSIS PATIENTS

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ABSTRACT
Background: Control of secondary hyperparathyroidism using active vitamin D analogues becomes difficult in advanced Secondary Hyperparathyroidism (SHPT) because enlarged glands (PTG) are resistant to medical treatment. So, intervention by Percutaneous Ethanol Injection Therapy (PEIT) are widely used. Objectives: The aim of this study is to evaluate the effect of parathyroid percutaneous ethanol injection therapy in treatment of hyperparathyroidism in CRF patients under haemodialysis.
Patients and methods: 45 end-stage renal diseased patients under regular haemodialysis were complained of secondary hyperparathyroidism, they were divided into two groups. these groups are group I including 15 patients treated by percutaneous ethanol injection therapy into parathyroid gland and group II subgrouped into A, B and C including 10 patients each in which group A was treated by calcitriol, group B was treated by calcimimetic and group C was treated by Sevelamer. Each group was followed up after treatment for detection of decreased parathyroid hormone, calcium, phosphorus and parathyroid gland size.
Results: In dialysis patients, there was a significant decrease in PTH, with improvement in serum calcium and phosphate. These results were significantly correlated with PTH levels and nodular volume. Patients under dialysis, with large nodule volume and very high PTH levels, obtained good results after PEIT. Conclusion: Treatment of patients of chronic renal failure who suffer from SHPT by percutaneous ethanol injection therapy was the most effective therapy.
Keywords: secondary hyperparathyroidism, percutaneous ethanol injection therapy, PTG

INTRODUCTION
Hyperparathyroidism is overactivity of the parathyroid glands resulting in excess production of parathyroid hormone (PTH). The parathyroid hormone regulates calcium and phosphate levels and helps to maintain these levels. Excessive PTH secretion may be due to problems in the glands themselves, in which case it is referred to as primary hyperparathyroidism and which leads to hypercalcemia. It may also occur in response to low calcium levels, as encountered in various situations such as vitamin D deficiency or chronic kidney disease; this is referred to as secondary hyperparathyroidism. In all cases, the raised PTH levels are harmful to bone, and treatment is often needed.

The kidney plays an important role in mineral metabolism; thus, in most chronic kidney disease (CKD) patients, various abnormalities of bone and mineral metabolism develop, depending upon the stage of the disease. It has been more widely recognized that deranged mineral metabolism in CKD results not only in bone diseases, but also in a higher risk of mortality, possibly through the development of vascular calcification.

Secondary hyperparathyroidism is one of the most common abnormalities of CKD-MBD. Secretion of parathyroid hormone (PTH) is usually stimulated without appropriate correction of hypocalcemia, hyperphosphatemia, and decreased production of 1,25- dihydroxyvitamin D in CKD patients. In such patients, parathyroid hyperplasia, composed of cells with a decreased density of vitamin D and calcium-sensing receptors, develops over the long term, which leads to resistance to medical therapy and the development of extrasosseous calcification.

Furthermore, medical therapy itself may worsen hypercalcemia and hyperphosphatemia in advanced cases. Thus, it is quite important to prevent the development of Parathyroid hyperplasia from the early stages of hyperparathyroidism.

The aim of this study is to evaluate the effect of parathyroid percutaneous ethanol injection therapy (PEIT) in treatment of hyperparathyroidism in CRF patients under haemodialysis.

PATIENTS AND METHODS
This study was carried out in Internal Medicine and Radiology Departments, in the period from 2007 to 2011.
Subjects: This study was conducted on 45 chronic dialysis patients. They were classified into the following groups:
Group (I): Fifteen patients treated by percutaneous Parathyroid Ethanol Injection (PEIT).
Group (II): Thirty patients treated by medical therapy. This group was subgrouped into A, B and C.
Group (A): Ten patients treated by calcitriol (0.05 µg daily).
Group (B): Ten patients treated by calcimimetics (cinacalcet), starting from 30 mg/day to be increased gradually up to maximum of 120 mg daily orally.
Group (C): Ten patients treated by phosphate binder (sevelamer hydrochloride) (400 to 800 mg orally daily).
All subjects included in this study fulfilled the following criteria.

They had symptoms of secondary HPT such as itching, bone joint pain, renal stone, nephrocalcinosis.

The long axis of parathyroid gland exceeded 5mm detected by Ultrasonography (U/S) and had positive blood flow by power Doppler U/S.

Serum ionized Ca > 10.5 mg/dl.

Serum phosphorous > 5.5 mg/dl.

Exclusion criteria for group I:

- Enlarged parathyroid gland located where ultrasonographic-guided puncture is impossible.
- Paralysis of the recurrent laryngeal nerve on the opposite side.
- Operation in the neck region for thyroid carcinoma, etc.

**Methods:**

All patients were subjected to:

- Through history taking and complete clinical examination.
- Routine Investigations:
  - Complete blood count.
  - Random blood sugar.
  - Liver function tests.
  - Kidney function tests.
- Specific investigations:
  - Serum calcium level by colorimetric method using automatic photometer (Behring- ELISA).
  - Serum phosphorus level by colorimetric method using automatic photometer (Behring- ELISA).
  - Assay of human intact parathyroid hormone.
  - Bone density measurement by DEXA scan (Norland Radiation) on lumbar spine (LS) and femoral neck (FN).
- Statistical analysis:
  - Mean, Standard Deviation (SD), Analysis Of Variance (ANOVA) and student “t” test were used for analysis of results of the present study (Epi-info version 14; Award processing data and statistics program for epidemiology on microcomputers. Centers for Disease Control. Altana, George, USA).

**RESULTS**

The mean serum calcium in all groups showed significant decrease after treatment (p < 0.05) except group IIa which showed significant increase in the mean serum calcium after treatment (p < 0.05) (table 1).

When the mean serum calcium was analyzed in various groups, there were intergroup significant differences, except when group IIc was compared with group I and group IIb. The differences were non-significant (table 2).

In table 3, the mean serum phosphorus in all groups showed significant decrease after treatment (p < 0.05) except in group IIa where the change of serum phosphorus was non-significant (p = 0.35).

In table 4, when the mean serum phosphorus was analyzed in various groups, there were intergroup significant differences, except when group IIc was compared with group I, the difference was non-significant.

The median serum PTH in all groups showed highly significant drop after treatment (p < 0.01) in all treatment groups except in group IIa where the drop of serum PTH was non-significant (p = 0.06) (table 5).

When the serum PTH was analyzed in various groups, there were intergroup non-significant differences, except when group I was compared with groups IIa, IIb and IIc, the difference of serum PTH was significant (p < 0.05) (table 6).

Table 7 presents the median size of parathyroid gland (in mm) in various treatment groups. There was highly significant decrease of parathyroid gland volume after treatment compared with that before treatment (p < 0.01), except in group IIa where the decrease in volume of parathyroid gland was non-significant (p = 0.06).

### Table (1): Mean ± Standard Deviation (SD) of serum calcium in groups; group I treated by PEIT and group II; IIa (treated by calcitriol), IIb (treated by cinacalcet) and group IIc (treated by sevelamer) at follow-up period

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum calcium Before treatment</th>
<th>After treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 15)</td>
<td>10.59 ± 0.22</td>
<td>9.79 ± 0.58</td>
<td>0.001 (HS)</td>
</tr>
<tr>
<td>IIa (n = 10)</td>
<td>10.56 ± 0.33</td>
<td>10.84 ± 0.15</td>
<td>0.02 (S)</td>
</tr>
<tr>
<td>IIb (n = 10)</td>
<td>10.54 ± 0.3</td>
<td>10.23 ± 0.62</td>
<td>0.03 (S)</td>
</tr>
<tr>
<td>IIc (n = 10)</td>
<td>10.67 ± 0.19</td>
<td>10.03 ± 0.42</td>
<td>0.03 (S)</td>
</tr>
</tbody>
</table>

### Table (2): Least Significant Difference (LSD) for comparison of several means among 4 groups at follow up

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>&lt; 0.05</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>IIc</td>
<td>&gt; 0.05</td>
<td>&lt; 0.001</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>
Table (3): The mean ± Standard Deviation (SD) of serum phosphorus in groups; group I (treated by PEIT) and groups IIa (treated by calcitriol), IIb (treated by cinacalcet) and group IIc (treated by sevelamer) at follow-up period

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum phosphorus</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>I (n = 15)</td>
<td>6.42 ± 0.21</td>
<td>5.46 ± 0.65</td>
</tr>
<tr>
<td>IIa (n = 10)</td>
<td>6.53 ± 0.14</td>
<td>6.6 ± 0.27</td>
</tr>
<tr>
<td>IIb (n = 10)</td>
<td>6.51 ± 0.16</td>
<td>6.01 ± 0.71</td>
</tr>
<tr>
<td>IIc (n = 10)</td>
<td>6.53 ± 0.12</td>
<td>5.46 ± 0.46</td>
</tr>
</tbody>
</table>

Table (4): Least Significant Difference (LSD) for comparison of several means among 4 groups at follow up

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>IIc</td>
<td>&gt; 0.05</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Table (5): The median and range of serum Parathyroid Hormone (PTH) in groups; group I (treated by PEIT) and groups IIa (treated by calcitriol), IIb (treated by clinacalcet) and group IIc (treated by sevelamer) at follow-up period

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum Parathyroid Hormone (PTH)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>I (n = 15)</td>
<td>745 (500-2050)</td>
<td>180 (150-2600)</td>
</tr>
<tr>
<td>IIa (n = 10)</td>
<td>898 (700-2000)</td>
<td>800 (500-2000)</td>
</tr>
<tr>
<td>IIb (n = 10)</td>
<td>942 (600-2000)</td>
<td>550 (200-1200)</td>
</tr>
<tr>
<td>IIc (n = 10)</td>
<td>700 (600-2000)</td>
<td>330 (200-2360)</td>
</tr>
</tbody>
</table>

Table (6): Least Significant Differences (LSD) for comparison of several medians of serum PTH among the 4 groups at follow up

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>&lt; 0.05</td>
<td>&gt; 0.05</td>
<td></td>
</tr>
<tr>
<td>IIc</td>
<td>&lt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Table (7): The median and range of size of parathyroid gland (in mm) in various groups before and after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Size of parathyroid gland</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>I (n = 15)</td>
<td>1000 (377-1380)</td>
<td>800 (230-2360)</td>
</tr>
<tr>
<td>IIa (n = 10)</td>
<td>965 (377-2000)</td>
<td>870 (370-2538)</td>
</tr>
</tbody>
</table>
DISCUSSION

SHPT is a serious complication of dialysis and can lead to renal osteodystrophy and other organ dysfunction. Renal osteodystrophy is associated with bone pain and reduced bone mass. The incidence of hip fracture is 85 times higher among dialysis patients compared with healthy individuals of the same age. With failing kidneys, the body has difficulty maintaining phosphorus levels within normal limits. Hyperphosphatemia promotes the development of parathyroid gland hyperplasia. 1,25-dihydroxyvitamin D synthesis, which is essential for the absorption of calcium, is decreased in patients with End-Stage Renal Disease (ESRD), which leads to hypocalcemia(4). In group I, patients were treated by PEIT, and reported decreased in PTH and improvement in serum calcium, phosphate, which was clearly correlated to basal PTH levels and to nodule volume. These results in agreement with that of Douthat et al.(5) who reported improvement of serum Ca, P, PTH and gland volume after PEIT.

Gland size is directly related to increased PTH secretion. It is possible that the better response in patients with higher basal PTH levels and larger glands was due to a better localization and optimized injection precision by ultrasonography. These results suggested that to obtain a good response to PEIT, patients should have big nodules and/or high basal PTH levels. (6)

In our study, all responsive patients showed symptomatic clinical improvement almost immediately after PEIT. Similarly, all patients with a positive symptomatic response to treatment represent an immediate decrease in PTH levels. In the present study, it was found that if more than one enlarged gland PEIT was ineffective in long term. This finding was consistent with the findings of Fukagawa et al.(7) who reported that selection of the optimal method for parathyroid intervention depends on the number and location of enlarged glands, as well as the presence of ectopic glands. As stated in the guidelines for selective PEIT, if three or more glands are enlarged to the dimensions specified, PEIT will probably ineffective in the long term.

Failure to PEIT could be related to a wrongly selection of gland for ethanol injection, poor results have been obtained in glands with difficult accessibility, diffuse hyperplasia, ectopic glands and ultrasonographic poor visibility (8).

In our study, the patients treated by vitamin D are resistant to treatment and also increase risk of hypercalcemia and hyperphosphatemia. These results were consistent with the results of Slatopolsky and Delmez(9) who reported that nodular hyperplasia is seldom responsive to intravenous vitamin D pulse therapy. So, early parathyroid intervention should be instituted.

In our study, patients treated with intravenous or oral vitamin D pulse therapy for 6 months and it is unsuccessful, there is a higher risk of ectopic calcification. These results were in agreement with Raggi et al.(10) who reported that traditional therapy, such as vitamin D sterols, remains suboptimal. It can cause hypercalcemia and creates a new set of problems, such as vascular and soft tissue calcification.

In our study, cinacalcet was more potent treatment for SHPT than calcitriol. It may be a more potent treatment for SHPT than active vitamin D analogues.

In our study, use of cinacalcet lead to significant decrease PTH level and also calcium and phosphorus showed significant decrease.

Similarly calcimimetics can completely suppress PTH hyperplasia and a significant inverse correlation between serum calcium levels and PTG cell number was observed after calcimimetic compound treatment(11).

In contrast to the present result, recently, an apparent hypercalcaemic condition produced by a calcimimetic compound, acting as a specific agonist of the parathyroid calcium receptor, inhibits the parathyroid cell proliferation occurring rapidly just after the ablation of renal function, despite the existence of long-lasting hyperphosphatemia.

In our study, patients treated by non-calcaemic phosphate binder (sevelamer) also effective in treatment of SHPT in ESRD.

Similarly, sevelamer suppressed the incidence of hyperphosphataemia by diminished gastrointestinal absorption of phosphorus as a phosphate binder, and did not affect serum calcium levels because it does not contain calcium. Therefore, serum calcium x phosphorus product paralleled serum phosphorus changes(11).

In our study, it was found that elevated serum phosphorus is the most important factor with the development of SHPT. Indeed, serum phosphorus levels correlated strongly with serum PTH levels. The lowered serum phosphorus levels by sevelamer treatment are considered to reduce serum PTH levels. However, these results were inconsistent with the results of Raggi et al. (12). Small hyperplastic parathyroid glands reportedly become smaller in response to cinacalcet administration, while nodular hyperplastic parathyroid glands do not.

Similarly, the effect of cinacalcet to shrink parathyroid glands was variable, and the effect of vitamin D must also be taken into consideration; in addition, for those in the gray area with PTH > 300 but < 500 pg/ml after cinacalcet treatment(12).

Calcimimetic agents are small organic molecules that activate the CaR in the membrane of the parathyroid cell, thereby inhibiting PTH release. They represent a novel approach to managing excess PTH secretion because their mechanism of action is distinct from that of the vitamin D sterols, and their efficacy in lowering plasma PTH concentrations in haemodialysis patients with secondary hyperparathyroidism has been documented in several clinical trials(14).

Similarly, in our study, in contrast to treatment with vitamin D analogues, serum calcium concentrations remain unchanged or decrease modestly during calcimimetic therapy, whereas serum phosphorus concentrations often decline. Thus, several biochemical abnormalities that have been associated with the development of soft tissue and vascular calcification in patients with ESRD improve as plasma PTH concentrations fall(14).

Similarly, apart from their immediate effect on PTH secretion, some studies suggest that calcimimetic compounds
retard the development of PTH hyperplasia signalling through the CaR by maintaining serum calcium concentrations within the normal range by dietary manoeuvres is also sufficient to prevent the development of parathyroid gland hyperplasia. Similarly, SHPT is managed successfully with medical treatment in most of the patients, but the disease becomes refractory to the therapy in a considerable number of them. This is more frequent in subjects with severe, long-term hyperparathyroidism and with nodular hyperplasia in enlarged glands. These glands have a lower density receptor for calcitriol and calcium both needed to respond to the treatment. Therefore, in these patients, it is necessary to consider the possibility of using invasive treatment.

Similarly, in several clinical settings, severe SHPT can be controlled quickly and safely by using PEIT. This technique is not only an alternative to surgical parathyroidectomy, but also an important adjunct to medical management. It has proved to be useful for patients on dialysis in circumstances in which the disease is considered to be resistant to medical treatment or when the surgical risk is high.

CONCLUSION
In dialysis patients, there was a significant decrease in PTH, with improvement in serum calcium and phosphate. These results were significantly correlated with PTH levels and nodular volume. Patients under dialysis, with large nodule volume and very high PTH levels, obtained good results after PEIT.

RECOMMENDATIONS
Our findings suggested that with the application of PEIT, patients respond satisfactorily if they present with high basal PTH levels and a considerable gland size. We propose to use it as a first step to control refractory secondary hyperparathyroidism. In other cases, the indications are less clear, but due to the low probability of complications, simplicity of the technique, and low cost, PEIT should be considered when nodular parathyroid enlargement is found on ultrasonographic examination.

REFERENCES
Poon G. Cinacalcet hydrochloride (Sensipar). Baylor University Medical Center (BUMC) 2005; 18: 181-184.