Assessment of ultrasound guided percutaneous ethanol injection and parathyroidectomy in patients with tertiary hyperparathyroidism

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Abstract

**Background.** Tertiary hyperparathyroidism continues to cause significant morbidity in patients with chronic renal failure. This is frequently resistant to medical management and may ultimately require a surgical parathyroidectomy. Recent studies have reported upon the technique of percutaneous ethanol ablation for both primary and tertiary hyperparathyroidism. In this study we report on a 5 year experience using ethanol injection and compare the results with surgical parathyroidectomy.

**Methods.** A prospective study in 39 patients with tertiary hyperparathyroidism, 25 were dialysis dependent and 14 had a functioning renal allograft. Twenty-two patients underwent percutaneous fine needle ethanol injection (PFNEI) and 17 underwent surgical parathyroidectomy.

**Results.** A >30% reduction in intact parathyroid hormone (iPTH) was achieved in 11 of 22 patients undergoing PFNEI after a mean of 1.8 ± 1.4 injections per gland. In four patients, symptomatic hyperparathyroidism recurred and they required further PFNEI or surgical parathyroidectomy at 17, 28, 46, and 48 months later. There was no significant reduction in iPTH in 11 patients following PFNEI after a mean of 2.5 ± 1.3 injections per gland. They all required a subsequent surgical parathyroidectomy for symptomatic hyperparathyroidism. Four patients developed a laryngeal nerve palsy following PFNEI, two of which were permanent. Seventeen patients underwent successful surgical parathyroidectomy as a primary procedure.

**Conclusion.** Whilst PFNEI is successful in primary hyperparathyroidism, when typically only one adenoma is present, the effectiveness of PFNEI is unpredictable and the long term results are poor compared with those of surgical parathyroidectomy in tertiary hyperparathyroidism. The procedure is not without complications and makes subsequent surgery more difficult. Therefore it can only be recommended for patients with a known single parathyroid gland such as patients in whom hyperparathyroidism has recurred following a previous surgical subtotal parathyroidectomy and who are unsuitable for further surgery.

**Key words:** chemical parathyroidectomy; percutaneous fine needle ethanol injection; tertiary hyperparathyroidism

Introduction

The pathogenesis of secondary hyperparathyroidism is being better understood as the interaction of calcium, phosphate, and calcitriol upon their specific receptors in the kidney, gut, and parathyroid glands are being elucidated [1–3]. Control of serum phosphate using dietary restriction, intestinal phosphate binders and dialysis, together with the use of 1,25 dihydroxyvitamin D3 may prevent the development of hyperparathyroidism in patients with end-stage renal failure [4–5]. Despite these measures, there may be continued hyperplasia of parathyroid glands, and a review of the European dialysis registry in 1989 revealed that 10–15% of haemodialysis patients required a parathyroidectomy after 10 years dialysis therapy [6].

Surgical parathyroidectomy is not without complication. Peri-operative morbidity including permanent laryngeal nerve palsy and symptomatic hypocalcaemia may occur [7,8]. Total parathyroidectomy may result in adynamic bone, whilst sub-total parathyroidectomy, introduced to avoid the consequences of total parathyroidectomy, exposes the patient to the risk of recurrence requiring further surgery [9].

Percutaneous fine needle ethanol injection (PFNEI) of the parathyroid glands was first reported by Solbiati et al. in 1985 [10]. This technique was developed following the observation that remission of hyperparathyroidism occurred in several patients following fine needle aspiration cytology, used for confirmation of parathyroid enlargement detected by ultrasound. Subsequent histology revealed extensive gland necrosis.
and haemorrhage. Excellent results have been reported using PFNEI in patients unsuitable for surgery with primary hyperparathyroidism and solitary glands [11,12]. Reports of the value of this technique in patients with secondary hyperparathyroidism are limited with relatively short follow-up [13,14]. In the largest reported series, Giangrande et al. reported a >30% reduction in C-terminal parathyroid hormone in 21 of 50 (42%) patients at 1 month, and 15 of 25 (60%) at 12 months [15]. The best results were obtained in those patients in whom hyperparathyroidism had relapsed following previous sub-total parathyroidectomy and who had a single enlarged gland. We report on the safety and efficacy of PFNEI in 22 selected patients with secondary hyperparathyroidism and compare the results with 17 patients who underwent surgical parathyroidectomy as a primary procedure.

**Subjects and methods**

In a 5 year period from August 1991 to August 1996, 39 patients, 17 women and 22 men mean age 48.6 ± 12.1 years, with severe hyperparathyroidism were assessed for PFNEI of their parathyroid glands. There were 25 dialysis patients (19 haemodialysis, 6 CAPD), and 14 patients with a functioning renal allograft. The causes of end-stage renal failure were: chronic glomerulonephritis (12), chronic interstitial nephritis + obstruction (9), congenital and polycystic (6), hypertension and renovascular (5), diabetes mellitus (2), and uncertain aetiology (5). There were four patients with recurrent hyperparathyroidism following a previous sub-total parathyroidectomy.

Patients were considered for intervention if they fulfilled one or more of the following criteria: the failure to suppress serum PTH to <750 pg/ml with optimal medical management (including pulsed calcitriol therapy), persistent hypercalcaemia (standard calcium > 2.9 mmol/l), or symptomatic bone pain.

Patients were selected for PFNEI or surgery according to the findings of their neck ultrasound. Patients were considered suitable for PFNEI if one or two glands >5 mm in diameter were identified. Glands <5 mm in diameter were not injected because the tip of the needle could not be accurately localised to the centre of the gland, with a consequent risk of extravasation of ethanol to surrounding tissue. In patients with one or two glands >5 mm but with additional glands <5 mm, the larger glands were injected and the patients treated with adjunct vitamin D therapy. Patients with three or four glands >5 mm were not offered PFNEI generally unless they were considered a high surgical risk or refused surgery. Absolute contra-indications to PFNEI were the presence of a multi-nodular goitre, deep localisation of the gland, or close proximity to a major vessel.

A serum aluminium was obtained on all patients and a low dose desferrioxamine (DFO) test (5 mg DFO/kg) was performed in those with concentration persistently >1.8 μmol/l [16]. Two patients had positive DFO tests, i.e. an increase in serum aluminium >2.0 μmol/l, and underwent right iliac crest bone biopsy. Histology revealed severe hyperparathyroid bone disease in both biopsies associated with severe aluminium deposition in one and mild deposition in the other. Both patients were given DFO chelation therapy until repeat DFO tests were negative. The patient with severe deposition was investigated with a repeat bone biopsy which confirmed successful mobilization and removal of aluminium. In both cases serum intact parathyroid hormone (iPTH) increased following treatment.

**Ethanol injection**

Ultrasound examination of the neck was performed using either an ATL Ultramark 9 or an Acuson 128XP ultrasound systems, with a 5–10 MHz transducers. Patients considered suitable for PFNEI were referred for indirect laryngoscopy to confirm cord movement, prior to undergoing ultrasound guided aspiration biopsy. Cytological examination and iPTH measurement of the needle washings were performed to confirm the presence of a functioning parathyroid adenoma.

Twenty-two patients were treated by PFNEI. Under direct-time ultrasound guidance, the tip of a 22 gauge needle was guided into the centre of the parathyroid gland. The volume of ethanol injected was calculated according to the volume of the gland (∼0.1 ml/mm³) to a maximum injection of 1 ml per treatment. An assessment of tissue destruction was made using colour Doppler blood flow mapping to assess the blood supply pre- and at 30 min post-injection. All patients suffered transient discomfort at the time of the injection, but the procedures were performed on an outpatient basis and all patients were able to return home.

Serum biochemistry was checked twice weekly for 1 month following the injection. If serum iPTH had not declined by >30% after one month, patients were referred for further PFNEI. Patients were referred for parathyroidectomy if, after a maximum of five injections, there was no significant reduction in serum iPTH or they refused further injections. Patients with a >30% reduction in serum iPTH but levels >200 pg/ml, were treated with adjunct vitamin D therapy. Calcitriol or alfacalcidol was given orally, as a daily or twice weekly pulsed regimen; doses were adjusted according to serum standard calcium and iPTH.

**Parathyroidectomy**

Seventeen patients were considered unsuitable for PFNEI; six patients had more than two glands detected on ultrasound, four had no parathyroid glands detected, and in three patients the glands identified were too small to inject. The presence of a multi-nodular goitre excluded two patients. Anatomical difficulties excluded one patient and one refused to undergo PFNEI after an aspiration biopsy, considering it too painful. All were referred for surgery with a total or subtotal parathyroidectomy performed according to operative findings.

**Biochemistry**

Serum calcium and total alkaline phosphatase (total ALP) were measured by autoanlyser (Hitachi autoanalyser Boehringer Mannheim). Standard calcium was calculated from the equation of Payne: standard calcium = Ca++ (40−albumin)×0.025 [17]. The iPTH was measured by radioimmunoassay (Nichols Institute Diagnostic Ltd) (normocalcaemic range 10–55 pg/ml).

**Statistical analysis**

All results are expressed as mean ± SD. Statistical analysis was performed using an ASTUTE statistical calculator computer program. Mann–Whitney and T-test were employed as
appropriate. A probability of <0.05 was considered statistically significant.

Results

Patients were classified as follows: Group A, 11 patients who underwent PFNEI with a >30% reduction in serum iPTH; group B, 11 patients who had a <30% reduction in serum iPTH, and who remained symptomatic despite repeated PFNEI and medical therapy, and therefore surgical parathyroidectomy was performed; group C, 17 patients who were considered unsuitable for PFNEI and were referred directly for surgical parathyroidectomy.

The ultrasonographic findings and pre-treatment serum biochemistry for the 22 patients who underwent PFNEI, and the preoperative biochemistry of the 17 patients in whom a surgical parathyroidectomy was performed, are shown in Table 1. The number of glands and the total volume of parathyroid tissue was greater in groups B than A, although this did not reach statistical significance ($P = 0.08$ and 0.06, respectively). Subsequent parathyroidectomy in those patients in group B resulted in the removal of an extra gland in two patients and two glands in six patients, which had not been detected on the initial ultrasound. There was no statistically significant difference in the serum iPTH, standard calcium, or total ALP between groups A, B, and C.

Group A

Table 2 shows the changes in the serum biochemistry of the 11 patients who had a >30% reduction in serum iPTH following a mean of 1.8 ± 1.4 injections per gland, which was associated with a significant decline in total ALP. In nine of these patients, there was a >50% reduction in serum iPTH, (746 ± 324 to 237 ± 198 pg/ml). Mean serum iPTH remained significantly lower than pre-treatment levels for 6 months following treatment. Symptomatic hyperparathyroidism recurred in four patients, who required further intervention at 17, 28, 46, and 68 months, respectively. Repeat PFNEI was successful in one of two patients but not attempted in the other two patients due to the presence of more than two glands. These three patients underwent successful sub-total parathyroidectomy. Histology revealed predominantly diffuse hyperplasia in two patients and nodular hyperplasia in a third. There were areas of dense fibrosis in the glands which had previously undergone PFNEI (Figure 1).

Group B

In these 11 patients, there was no significant change in serum iPTH following a mean of 2.5 ± 1.3 injections per gland. They all subsequently required a surgical parathyroidectomy. Table 3 shows the serum biochemistry pre- and post-ethanol injection and pre- and post-parathyroidectomy. There was no significant difference in serum biochemistry pre-PFNEI or pre-parathyroidectomy. Four patients underwent total, and seven underwent sub-total parathyroidectomy. There was a highly significant reduction in serum standard calcium, iPTH, and total ALP following parathyroidectomy. Histology revealed five patients with predominantly diffuse hyperplasia, two with mixed diffuse and nodular hyperplasia and four patients with predominantly nodular hyperplasia. There were areas of dense fibrosis in the glands that had undergone previous PFNEI.

Group C

Seventeen patients considered unsuitable for PFNEI were referred for surgical parathyroidectomy, five of whom underwent a total, and 12 underwent sub-total parathyroidectomy. Table 4 shows the changes in the serum biochemistry following parathyroidectomy with highly significant reductions in standard calcium, iPTH, and total ALP. Histology revealed six patients with predominantly diffuse hyperplasia, eight with mixed diffuse and nodular hyperplasia, and three patients with predominantly nodular hyperplasia.

<table>
<thead>
<tr>
<th>Table 1. Ultrasound findings and pre-treatment serum biochemistry mean ± SD</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
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</tbody>
</table>

Group A, patients with a >30% reduction in iPTH following PFNEI.
Group B, patients with no reduction in iPTH following PFNEI.
Group C, patients undergoing surgical parathyroidectomy as a primary procedure.
Table 2. Group A, changes in serum biochemistry in the 11 patients who had a >30% reduction in iPTH following PFNEI of their parathyroid glands.

<table>
<thead>
<tr>
<th>Time in months following ethanol</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Standard calcium (mmol/l)</td>
<td>2.78 ± 0.22</td>
<td>2.67 ± 0.21</td>
<td>2.67 ± 0.21</td>
<td>2.6 ± 0.06</td>
<td>2.58 ± 0.21</td>
<td>2.68 ± 0.05</td>
<td>2.73 ± 0.04</td>
<td>2.54 ± 0.15</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>734 ± 330</td>
<td>266 ± 202***</td>
<td>324 ± 224**</td>
<td>377 ± 233**</td>
<td>686 ± 539</td>
<td>489 ± 378</td>
<td>455 ± 269*</td>
<td>89 ± 76</td>
</tr>
<tr>
<td>Total ALP (IU/l)</td>
<td>413 ± 236</td>
<td>335 ± 240*</td>
<td>362 ± 367</td>
<td>285 ± 250</td>
<td>285 ± 214</td>
<td>259 ± 156*</td>
<td>292 ± 256</td>
<td>163 ± 47</td>
</tr>
</tbody>
</table>

Paired t-test P-values P < 0.05*; P < 0.01**; P < 0.001***.

Colour Doppler blood flow mapping

Blood flow mapping was undertaken to assess tissue destruction. A marked reduction in blood flow was recorded in all glands following treatment (Figure 2). In those patients who subsequently required surgical parathyroidectomy, histology revealed significant fibrosis in the glands treated previously. A reduction in Doppler blood flow following injection confirmed tissue destruction but was unable to distinguish between those patients who would have responded to PFNEI and those who would not.

In those patients requiring subsequent parathyroidectomy, local dissection was extremely difficult in the areas of previous ethanol injection due to dense local fibrosis presumably from local ethanol extravasation. One patient who had suffered permanent laryngeal nerve palsy following PFNEI and needed a surgical parathyroidectomy subsequently, developed severe stridor post-operation, requiring re-intubation and subsequent transfer to the Intensive Care Unit for 48 h observation. There were no reported complications with the patients who underwent primary surgical parathyroidectomy.

Complications

All patients described a transient local burning sensation as the ethanol was injected into the parathyroid glands. Two patients suffered transient laryngeal nerve palsy and in a further two patients it was permanent.

In this study, we found 11 of 22 (50%) patients had a >30% reduction in serum iPTH after an average of 1.8 ± 1.4 ethanol injections per gland. Giangrande *et al*. reported similar results: 21 of 50 (42%) patients with...
Percutaneous ethanol injection and parathyroidectomy treatment of hyperparathyroidism

Table 3. Group B, changes in serum biochemistry in the 11 patients who had no significant reduction in iPTH following PFNEI and subsequently required a surgical parathyroidectomy

<table>
<thead>
<tr>
<th>Time in months following parathyroidectomy</th>
<th>n</th>
<th>Time in months following ethanol injection</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-parathyroidectomy</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Standard calcium (mmol/l)</td>
<td>2.86±0.24</td>
<td>2.82±0.24</td>
<td>2.88±0.28</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>856±554</td>
<td>843±473</td>
<td>812±220</td>
</tr>
<tr>
<td>Total ALP (IU/l)</td>
<td>395±260</td>
<td>412±276</td>
<td>412±276</td>
</tr>
<tr>
<td>Post-parathyroidectomy, test P-values</td>
<td>P&lt;0.05</td>
<td>P&lt;0.01</td>
<td>P&lt;0.01***</td>
</tr>
</tbody>
</table>

Table 3 continued...

The greatest success rate appears in those studies with the shortest time intervals between injections. Karstrup et al. in a prospective study of patients with primary hyperparathyroidism injected 14 patients at weekly intervals and another 18 patients at monthly intervals [12]. Hyperparathyroidism was controlled in 11 (79%) patients injected weekly compared with 12 (66%) patients injected monthly. In a further study of primary hyperparathyroidism, seven patients were injected at 24 h intervals to a single parathyroid adenoma [11]. Serum iPTH declined to normal in six of seven patients following two or three injections. The only treatment failure had two parathyroid glands removed at parathyroidectomy, one of which had not been detected by ultrasound. In patients with secondary hyperparathyroidism, Kitaoka et al. reported a high success rate when patients were injected at weekly intervals until their serum iPTH was <200 pg/ml [14]. In our study, we aimed to perform subsequent injections, if required, within 1 month, although there were patients in whom this time interval was greater.

The volume of ethanol injected does not appear to alter success rate of this procedure, but large volumes may increase the risk of collateral damage. Despite being injected into the centre of the gland, ethanol does not diffuse uniformly and will follow the line of least resistance, resulting in extravasation from the gland and damage to adjacent tissue. Histology of the parathyroid tissue removed from patients in whom PFNEI was not successful revealed large fibrous bands with compartments of parathyroid tissue. Once compartmentalisation has occurred, it is unlikely that subsequently the needle will puncture directly, or ethanol diffuse into, all of the pockets of remaining parathyroid tissue. The greatest reported success rates have been obtained with a modified needle which promotes diffusion throughout the gland, with injections repeated at weekly intervals [14]. In this study, PFNEI failed to suppress the iPTH in 50% of the patients. Colour Doppler blood flow mapping revealed a significant reduction in the blood supply in the glands injected of both responders and non responders (Figure 2). The failure in these patients was probably not of the technique to destroy the gland injected but the inability to detect with ultrasound all the hyperplastic glands present, resulting in poor patient selection. Subsequent parathyroidectomy in those patients in group B resulted in the removal of an extra gland in two patients and two glands in six patients, which had not been detected on the initial ultrasound. In the four patients in Group C referred for parathyroidectomy because no discernible gland was detected on ultrasound, the authors performed a further 14 injections using a modified injection needle with a blind tip and three side holes to improve ethanol dispersion [14]. They performed 32 injections in 16 parathyroid glands in eight patients with a >30% reduction in iPTH in all patients.

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Table 4. Group C, changes in serum biochemistry in the 17 patients undergoing surgical parathyroidectomy as a primary procedure.

<table>
<thead>
<tr>
<th>Time in months following parathyroidectomy</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
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<tr>
<td>0</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>15</td>
<td>14</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Standard calcium (mmol/l)</td>
<td>2.88 ± 0.27</td>
<td>2.31 ± 0.36**</td>
<td>2.45 ± 0.34**</td>
<td>2.56 ± 0.25**</td>
<td>2.45 ± 0.24**</td>
<td>2.45 ± 0.13***</td>
<td>2.6 ± 0.19</td>
<td>2.27</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>653 ± 559</td>
<td>34 ± 52***</td>
<td>40 ± 45**</td>
<td>42 ± 47**</td>
<td>38 ± 36**</td>
<td>60 ± 81***</td>
<td>138 ± 237**</td>
<td></td>
</tr>
<tr>
<td>Total ALP (IU/l)</td>
<td>505 ± 559</td>
<td>475 ± 379*</td>
<td>231 ± 177**</td>
<td>178 ± 977*</td>
<td>178 ± 95*</td>
<td>180 ± 141*</td>
<td>160 ± 52*</td>
<td>242</td>
</tr>
</tbody>
</table>

Paired t-test P-values: *P < 0.05; **P < 0.01; ***P < 0.001.

Giagrande et al. advocated that in patients with moderate hyperparathyroidism, PFNEI could reduce PTH and calcium allowing vitamin D therapy to be used more effectively [15]. In this study, adjunct vitamin D therapy failed to prevent the recurrence of symptomatic hyperparathyroidism in four of the 11 patients who initially responded to PFNEI, due to the continued hyperplasia of cells in both injected and non-injected glands. Hyperplasia continues in these patients in part due to the marked reduction in the expression of the vitamin D receptor in uraemic parathyroid tissue [21].

could be identified with ultrasound, a total of 12 glands were removed at the time of surgery. The detection of parathyroid hyperplasia relies upon both a change in the echogenic properties of the cells as well as gland enlargement [18]. Ultrasonography does not detect all enlarged parathyroid glands, but its success rate is comparable with other techniques, in primary hyperparathyroidism, e.g. thallium technetium subtraction scanning [19]. Higher detection rates have been reported recently in tertiary hyperparathyroidism with Technetium-99m methoxy isobutyl isonitrile (Tc MIBI) imaging [20].

Fig. 2. Doppler blood flow mapping of a parathyroid gland, showing the blood supply pre-injection (left photograph) is virtually obliterated 30 min post-injection (right photograph).
Percutaneous ethanol injection and parathyroidectomy treatment of hyperparathyroidism

The best results in this study were obtained in patients who had previously undergone subtotal parathyroidectomy and required injection into a single gland. Three of these patients had a >50% fall in serum iPTH following one, two, and four injections per gland, respectively. There was long-term control of their hyperparathyroidism with serum iPTH falling from 892 ± 170 pg/ml pre-treatment to 377 ± 305 pg/ml 36 months after injection. The fourth patient required a parathyroidectomy after four injections had failed to alter the serum iPTH. Giangrande et al. reported a similar ‘golden subgroup’ [15]. There was no significant difference in the success rate of PFNEI to control hyperparathyroidism in either transplanted or dialysis patients.

In conclusion, whilst PFNEI is successful in primary hyperparathyroidism when typically only one adenoma is present, the effectiveness of PFNEI is unpredictable and the long term results are poor compared with those of surgical parathyroidectomy in tertiary hyperparathyroidism. The procedure is not without complications and makes subsequent surgery more difficult. Therefore, it can only be recommended for patients with a known single parathyroid gland, such as patients in whom hyperparathyroidism has recurred following a previous surgical subtotal parathyroidectomy and who are unsuitable for further surgery.

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