Results of ultrasonically guided percutaneous ethanol injection into parathyroid adenomas in primary hyperparathyroidism

Bruno I. Vergès, Jean P. Cercueil, Denis Jacob, Geneviève Vaillant, Jean M. Brun and Roger Putelat
Department of Endocrinology and Department of Radiology, University Hospital, Dijon, France


Surgery is the usual treatment for primary hyperparathyroidism. However, some patients with high surgical risks are not suitable for surgery. For such patients, we propose, as an alternative treatment, ultrasonically guided percutaneous ethanol injection into parathyroid adenomas, in order to induce necrosis of the tumor. We report, here, the results of ultrasonically guided percutaneous ethanol injection into parathyroid adenomas, during a prolonged follow-up period up to 49 months, in a group of 13 patients (median age 79 years) with primary hyperparathyroidism and contraindications for surgery. In seven patients, complete normalization of plasma calcium, phosphorus and parathyroid hormone (PTH) levels was achieved after ethanol injections, with no recurrence of hypercalcemia during a median follow-up period of 28 months (total success). In these seven patients, plasma calcium, phosphorus and PTH levels were normalized 48 h after the successful ethanol injection. In four patients, a partial success was obtained with clinical improvement and normalization of plasma calcium levels but without complete normalization of plasma PTH levels. This partial success is due to incomplete necrosis of the adenoma, as has been confirmed in one patient by histopathological examination. The ethanol injection treatment failed in only two patients. This treatment was always well tolerated and no major side-effects were observed. In conclusion, our results give evidence that ultrasonically guided percutaneous ethanol injection into parathyroid adenomas can be a very useful alternative therapy in patients not suitable for surgery.

Bruno Vergès. Service d’Endocrinologie. Hôpital du Bocage, BP 1542, 21 034 Dijon, France

It is generally agreed that patients with primary hyperparathyroidism require surgery (1). However, surgery is sometimes unadvisable in patients with high surgical risks. During the last few years ultrasonically guided percutaneous injection of ethanol into parathyroid adenomas has been proposed as an alternative treatment, more specifically for patients not suitable for surgery (2–5). Ultrasonically guided ethanol injection has been shown to be successful in the treatment of parathyroid tumors in secondary hyperparathyroidism (6). A few cases of successful treatment of primary hyperparathyroidism by ultrasonically guided ethanol injection have been reported (2, 3). The short-term results of this treatment for primary hyperparathyroidism have been reported by Karstrup et al. (4).

To evaluate the advantages and the limitations of this new procedure, we present here the results of ultrasonically guided percutaneous ethanol injection into parathyroid adenomas in a group of patients with primary hyperparathyroidism, during a prolonged follow-up period up to 49 months.

Patients and methods

Thirteen patients (median age 79 years, range 66–98 years) with confirmed primary hyperparathyroidism were selected for treatment by ultrasonically guided percutaneous ethanol injection of parathyroid adenomas. All patients but one had contraindications for surgery (severe heart failure: 7, recent myocardial infarction: 4, recent stroke: 1) at the time of treatment by ultrasonically guided ethanol injection.

The main clinical features of primary hyperparathyroidism, for each patient, are shown in Table 1. Prior to treatment, all patients had elevated plasma ionized calcium levels, decreased plasma phosphorus levels and increased plasma intact PTH (1–84) levels, as shown in Table 2.

All patients had ultrasound visualization of a parathyroid tumor. The volumes of parathyroid tumors were measured as half of the product of maximum length, width and depth. The volumes of the parathyroid tumors ranged from 0.11 to 4.18 ml (Table 1).

Ultrasonic scanning was performed with a dynamic 5-MHz sector scanner (Kontron Instruments, Montigny Le Bretonneux, France) mounted with a needle-steering device for precise placement of needles. The ultrasound transducer was used through a sterile glove. The skin was cleansed with povidone iodine and sterile gel served as an acoustic coupler. With use of local anesthesia, a 20-gauge needle was inserted in the parathyroid tumor, under complete ultrasound control. When the needle-tip
Table 2. Plasma-ionized calcium, total calcium, phosphorus and PTH levels in each patient before treatment.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Ionized calcium (mmol/l)</th>
<th>Phosphorus (mmol/l)</th>
<th>PTH (pmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1.12-1.38)</td>
<td>(0.80-1.53)</td>
<td>(1.05-6.82)</td>
</tr>
<tr>
<td>1</td>
<td>1.68</td>
<td>0.64</td>
<td>29.29</td>
</tr>
<tr>
<td>2</td>
<td>1.92</td>
<td>0.51</td>
<td>24.15</td>
</tr>
<tr>
<td>3</td>
<td>1.65</td>
<td>0.64</td>
<td>16.27</td>
</tr>
<tr>
<td>4</td>
<td>1.85</td>
<td>0.96</td>
<td>12.81</td>
</tr>
<tr>
<td>5</td>
<td>1.57</td>
<td>0.64</td>
<td>11.76</td>
</tr>
<tr>
<td>6</td>
<td>1.53</td>
<td>0.80</td>
<td>11.23</td>
</tr>
<tr>
<td>7</td>
<td>1.55</td>
<td>0.96</td>
<td>12.07</td>
</tr>
<tr>
<td>8</td>
<td>1.59</td>
<td>1.10</td>
<td>8.61</td>
</tr>
<tr>
<td>9</td>
<td>1.80</td>
<td>0.80</td>
<td>19.74</td>
</tr>
<tr>
<td>10</td>
<td>1.76</td>
<td>0.70</td>
<td>38.22</td>
</tr>
<tr>
<td>11</td>
<td>1.60</td>
<td>0.89</td>
<td>11.23</td>
</tr>
<tr>
<td>12</td>
<td>1.62</td>
<td>0.76</td>
<td>13.86</td>
</tr>
<tr>
<td>13</td>
<td>1.88</td>
<td>0.62</td>
<td>18.69</td>
</tr>
</tbody>
</table>

Median (range) 1.65 (1.53-1.92) 0.76 (0.51-1.10) 13.86 (8.61-38.22)

* Normal range.

echo was seen inside the parathyroid tumor. 0.5–1 ml of 95% ethanol was injected. At the moment of injection, the tumor became highly echogenic (Fig. 1). The dose of ethanol used for each injection was the quantity needed to obtain a hyperchogenic tumor. The patient was required to speak during ethanol injection to be sure of the recurrent laryngeal nerve integrity.

One to eight ethanol injections were performed in each patient (Table 1). When more than one injection was needed, ethanol injections were separated by short intervals of 3–8 days. Plasma-ionized calcium and phosphorus levels were evaluated 2, 6, 24 and 48 h after each ethanol injection. Plasma PTH levels were measured 48 h after each ethanol injection. When ionized calcium had normalized, no further ethanol injection was performed. After the last ethanol injection, ionized calcium, phosphorus and PTH levels were measured every month up to 3 months and then every 6 months.

Ionized calcium was measured at pH 7.40 by an ionized calcium analyzer (ICA₂, Radiometer, Copenhagen, Denmark). The plasma phosphorus level was measured by an ultraviolet photometric assay (Eris Olympus analyser, Eppendorf, Hamburg, Germany). The determination of plasma PTH was performed as intact PTH (1–84) using a radioimmunoassay (Allegro intact PTH, Nichols Institute, San Juan Capistrano, CA, USA).

Results were expressed as median and range. Comparisons were performed using the non-parametric Wilcoxon’s test for paired data. p values are two-tailed.

Results

The result of the ultrasound-guided ethanol injection treatment was considered as a “total success” when complete normalization of calcium and PTH levels was
**Fig. 1.** (A) Ultrasound transverse view of a parathyroid adenoma before ethanol injection. The parathyroid adenoma (black arrow) is hypoechogenic. (B) Ultrasound transverse view 48 h after ethanol injection. The parathyroid adenoma (black arrow) has become hyperechogenic.

![Ultrasound images](image1.png)

**Fig. 2.** (A) Plasma PTH levels before and after ethanol injection (1 month later and last measurement) in the 13 patients: □ patients with "total success"; ▲ patients with "partial success"; ○ patients with "failure". (B) Plasma-ionized calcium levels before and after ethanol injection (1 month later and last measurement) in the 13 patients: □ patients with "total success", ▲ patients with "partial success", ○ patients with "failure".

![Plasma hormone levels](image2.png)

**Table 3.** Median and range (mmol/l) of plasma-ionized calcium, total calcium, phosphorus and PTH levels before and after the last ethanol treatment in the seven patients from the "total success" group.

<table>
<thead>
<tr>
<th></th>
<th>Before injection (mmol/l)</th>
<th>2 h</th>
<th>6 h</th>
<th>24 h</th>
<th>48 h</th>
<th>1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-ionized calcium</td>
<td>1.80 (1.53–1.92)</td>
<td>1.55 (1.36–1.65)</td>
<td>1.52 (1.35–1.58)</td>
<td>1.36 (1.29–1.40)</td>
<td>1.28** (1.18–1.32)</td>
<td>1.25** (1.20–1.31)</td>
</tr>
<tr>
<td>Plasma phosphorus</td>
<td>0.76 (0.51–0.96)</td>
<td>0.87 (0.60–0.99)</td>
<td>0.89 (0.63–1.12)</td>
<td>1.07** (0.87–1.30)</td>
<td>1.12** (0.90–1.31)</td>
<td></td>
</tr>
<tr>
<td>Plasma PTH (1–84)</td>
<td>16.27 (11.23–24.15)</td>
<td></td>
<td></td>
<td></td>
<td>5.30** (4.10–6.12)</td>
<td>5.56** (4.20–6.40)</td>
</tr>
</tbody>
</table>

**p <0.01**: comparison of plasma calcium, phosphorus and PTH levels before vs 48 h after ethanol injection or before vs 1 month after ethanol injection.
Fig. 3. Histopathology of a parathyroid adenoma in a patient with partial success of the ethanol injection treatment who underwent surgery.
*: A necrosed area of the adenoma; **: fibrosis; ***: remaining functional parathyroid tissue. (Hematoxylin & eosin; (A) 40 ×, (B) 250 ×.)
observed in the patient after treatment. The result was considered as a "partial success" when significant clinical improvement and normalization of plasma calcium level occurred in the patient after ethanol injection treatment, but with persistent elevated PTH levels. When no significant changes of plasma calcium levels were observed in the patient, the result was considered as a "failure". Among the 13 treated patients, we observed seven cases of "total success", four cases of "partial success" and two cases of "failure".

Plasma PTH and ionized calcium levels before ethanol injection and after ethanol injection treatment (1 month later and last measurement) in the 13 patients are shown in Fig. 2.

**Total success**

In seven patients (nos 2, 3, 4, 6, 9, 12 and 13), the ultrasound-guided ethanol injection treatment was totally successful with complete normalization of plasma calcium and PTH levels. In these patients, plasma calcium and PTH levels remained normal to date, during a median follow-up period of 28 months (range 1.5–49 months). One to three ethanol injections were needed in these seven patients in order to obtain complete normalization of plasma calcium and PTH levels.

Plasma-ionized calcium and phosphorus levels 2.6, 24 and 48 h and 1 month after the last ethanol injection in the seven successfully treated patients are shown in Table 3. Plasma calcium and PTH levels were reduced significantly (p<0.01) and plasma phosphorus levels increased significantly (p<0.01) after ethanol injection (Table 3). Interestingly normalization of plasma calcium and phosphorus levels was observed 48 h after the successful ethanol injection in each patient. The PTH levels were normal 48 h after the successful ethanol injection. Calcium, phosphorus and PTH levels 48 h after the successful ethanol injection were not significantly different from those observed 1 month after injection (Table 3).

Among these seven successfully treated patients, one (no. 2) presented with an acute hyperparathyroid crisis. Although this patient was treated intensively with infusion of calcium-lowering agents, she remained in a life-threatening state. This patient was dramatically improved (clinically and biologically) 24 h after the ultrasonically guided ethanol injection.

**Partial success**

In four patients (nos 1, 8, 10 and 11), clinical improvement and normalization of plasma calcium levels were observed after ethanol injection. However, plasma PTH levels, although significantly decreased, remained elevated in these patients. Thus, these four cases were considered as a partial success.

Among these patients, one (no. 1) had an acute parathyroid crisis before treatment. This patient was dramatically improved 48 h after the third ethanol injection as the plasma calcium level was normalized. Because of the still elevated plasma PTH levels, although plasma-ionized calcium levels were normal (1.32 mmol/l), a recurrence of hypercalcemia was feared in this patient and neck surgery was decided. An excessive amount of fibrosis surrounding the parathyroid tumor was found in this patient, making the surgical treatment unusually difficult. Histopathological examination of the tumor revealed uncompleted necrosis of a parathyroid adenoma with remaining functional parathyroid tissue inside the tumor (Fig. 3).

The three other patients are still normocalcemic with a median follow-up period of 20 months (range 10–29 months).

**Failure**

The ethanol injection treatment failed in two patients (nos 5 and 7). These two patients had persistent hypercalcemia after ethanol injection. The two patients underwent surgery 3 months (no. 5) and 7 months (no. 7) following injection therapy. In both cases, a parathyroid adenoma surrounded by fibrosis was found.

**Side effects**

Transient dysphonia was noted in four patients. Dysphonia occurred during the ethanol injection and lasted only a few minutes in three patients and 1 month in the other. Indirect laryngoscopy was performed in these four patients and no vocal cord paralysis was observed. No other side-effects have been noted. The treatment was always well tolerated and the patients did not complain about pain in the neck or towards the jaws, either during ethanol injection or during the days after injection.

**Discussion**

Surgery is the recommended treatment for primary hyperparathyroidism. Surgical parathyroidectomy is generally safe. However, old patients and patients with chronic disease represent a high surgical risk group (7, 8). For such patients who are not suitable for surgery, alternative treatments may be considered. Angiographic embolization of parathyroid adenomas by contrast material or gel-foam has been proposed in adenomas within the mediastinum (9, 10). Parathyroid surgery under regional anesthesia has been performed in a few patients (11). For a few years, ultrasonically guided percutaneous ethanol injection into parathyroid adenomas has been proposed as an alternative treatment for patients at high surgical risk (2–5). Injection of ethanol has been used as a therapeutic mode for renal and hepatic tumors (12, 13), for esophageal varices (14) and
more recently for treatment of autonomous thyroid nodules (15). Injection of ethanol into a tumor leads to its infarction.

In the present study, results of ultrasonically guided percutaneous ethanol injection into parathyroid tumors in a group of patients with primary hyperparathyroidism, during a prolonged follow-up period, are reported. This treatment failed in only two patients among 13 (15%), with total success achieved in seven patients (54%) and partial success in four patients (31%).

In the “total success” group, plasma calcium and PTH levels still remain normal. We can consider that, in these patients, the hyperactive parathyroid tumors were totally inactivated following ethanol injections.

In four patients (31%), partial success was achieved with clinical improvement and normalization of the plasma calcium level. But plasma PTH levels remained slightly elevated in these patients, who are at risk for recurrence of hypercalcemia in the future. However, this treatment was considered helpful because of the clinical benefit obtained in these old patients. The partial success can be explained by an incomplete necrosis of the tumor. Indeed, histopathological examination of a parathyroid tumor in one patient with “partial success” who underwent surgery revealed incomplete necrosis of the parathyroid adenoma with persistent parathyroid tissue inside the tumor. Further ethanol injections can be proposed for these patients with “partial success” in order to complete the adenoma necrosis.

Among the 13 treated patients, two presented with an acute hyperparathyroid crisis. One patient was completely cured after ethanol injection treatment. The other patient, although normocalcemia, had still slightly elevated plasma PTH levels after ethanol injection. However, in this patient, ethanol injection treatment has been able to restore a good clinical condition, suitable for surgery, when a surgical treatment could not have been performed during the hyperparathyroid crisis. Thus, ethanol injection treatment may be very helpful in patients with hyperparathyroid crisis.

In our series of patients, ethanol injection was always well tolerated without any local pain. Transient local pains have been reported after ethanol injection into thyroid nodules (19) and into parathyroid tumors (6) when more than 1 ml of alcohol had been injected. We anticipate that the injection of large volumes of ethanol are likely to promote more frequently the occurrence of local pain after injection. The volume of ethanol injected into the parathyroid tumor in our patients never exceeded 1 ml, which can explain the absence of local pain in our series. Potential morbidity associated with alcohol injection of parathyroid adenomas can include permanent damage to the recurrent laryngeal nerve (4), which is the reason why our patients were required to speak during ethanol injection in order to detect dysphonia. Dysphonia during ethanol injection occurred in four patients, leading us to stop the ethanol injection immediately. Dysphonia was transient in these patients and none of them had vocal cord paralysis. We feel that ethanol injection has to be stopped as soon as dysphonia occurs. In order to prevent permanent recurrent laryngeal nerve paralysis. Dysphonia can be detected easily when the patient is required to speak during ethanol injection.

The three patients operated on were found to have fibrosis surrounding the tumor, most likely due to ethanol diffusion outside the tumor capsule. As reported previously by Karstrup et al. (4), this fibrosis made neck surgery unusually difficult.

When ethanol injection was successful, normalization of plasma calcium and phosphorus levels was observed 48 h later. This indicates that complete necrosis of the tumor does not occur immediately after ethanol injection but more progressively over a period of several hours after injection. In our experience, plasma calcium and phosphorus measurements 48 h after ethanol injection are good indicators for success or failure. When calcium and phosphorus level normalization is not achieved 48 h after ethanol injection, the patients undergo another ultrasonically guided percutaneous ethanol injection in order to complete the tumor necrosis. Plasma calcium and phosphorus measurements 48 h after ethanol injection are very useful and are an interesting way to reduce intervals between ethanol injections when more than one ethanol injection is needed. Indeed, the intervals between ethanol injections should not be too long, in order to avoid the occurrence of fibrosis. Such fibrosis could make further ethanol injections more difficult.

In the seven patients who were treated successfully, one to three ethanol injections were needed but never more than three injections. This tends to show that, in the case of failure after three ethanol injections, it may not be useful to carry on injecting ethanol into the tumor.

Interestingly, the success of ethanol injection therapy does not depend on the size of the tumor. The reasons for these discrepancies between the size of the tumor and the chances of success are not clear. In order to explain these results, we hypothesize that, in the case of success, ethanol injection could provoke necrosis of an area close to the afferent artery of the tumor, leading to a secondary ischemic necrosis of the rest of the tumor.

In conclusion, the long-term results of our patients with primary hyperparathyroidism treated by ultrasonically guided percutaneous ethanol injection give evidence that this new treatment can be a very useful alternative therapy in patients not suitable for surgery. Hyperparathyroidism was completely cured after ethanol injection in 54% of the patients. Thirty-one per cent of the patients were clinically improved and normocalcemia after ethanol injection, but still had slightly elevated PTH levels. This partial success is due to incomplete necrosis of the adenoma. Plasma calcium and phosphorus levels 48 h after the ethanol injection are good indicators for success or failure.
References


Received March 3rd, 1993
Accepted June 2nd, 1993