Effectiveness of Percutaneous Ethanol Injection Therapy in Benign Nodular and Cystic Thyroid Diseases: Long-term Follow-up Experience

SEONG JIN LEE AND IL-MIN AHN*

Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, Hallym University, ChunCheon 200-704, South Korea
*Chung Dam Institute of Thyroid Clinic and Research, Seoul 135-090, South Korea

Abstract. This study was designed to clarify the long-term efficacy and safety of percutaneous ethanol injection (PEI) therapy in benign nodular and cystic thyroid diseases, and to evaluate response by criteria defined as disappearance of hot nodule. Solid nodule and complex cyst were classified into three groups in accordance with volume reduction. In autonomously functioning thyroid nodule (AFTN), disappearance of hot nodule with normalization of thyroid hormone level and restored extra-nodular uptake was defined to be curative. In solid nodule (n = 198) and complex cyst (n = 432), initial volume was significantly reduced to post-PEI and final volumes, and volume reduction persisted during follow-up period. Complete response, partial response and no response were as follows: 17.2%, 71.7%, 11.1% in solid nodule; 19.0%, 60.4%, 20.6% in complex cyst, respectively. Differences of volume reduction according to initial volume (≥10 mL vs. <10 mL) were significant. Correlations between initial and final volumes, and between initial volume and volume reduction were also significant. In 24 patients with AFTN, when effectiveness was assessed by disappearance of hot nodule, only 1 case was curative. Reexpansion or recurrence was observed in 5 cases. Complications developed in 9.0% but there was no permanent or serious complication in this study. In conclusion, our data suggest that PEI therapy could be an effective and safe therapeutic modality for benign nodular and cystic thyroid diseases especially when initial volume is more than 10 mL, but may not induce disappearance of hot nodule itself in AFTN.

Key words: Percutaneous ethanol injection, Solid nodule, Complex cyst, Autonomously functioning thyroid nodule

IN benign thyroid solid nodule, thyroid hormone suppressive therapy may be performed but its efficacy and safety are still controversial [1]. Although surgical treatment is curative especially in large-sized nodule, it has disadvantages including general anesthesia, postoperative scar formation and iatrogenic hypothyroidism. In benign thyroid complex cyst, thyroid hormone suppressive therapy is known to have little effect, and therefore surgical excision is usually chosen when the cyst compresses adjacent structures or causes cosmetic problems [2–4]. The mainstay treatment for autonomously functioning thyroid nodule (AFTN) is radioactive iodine ablation or surgery [5, 6]. However, radioactive iodine ablation requires special equipment and surgery is often complicated.

Percutaneous ethanol injection (PEI) therapy is a procedure to treat various types of benign and malignant neoplasm [7–10]. Since PEI therapy in benign nodular and cystic thyroid diseases was introduced, it has drawn attention as a novel therapeutic modality although its efficacy and safety are under debate [11–14]. If PEI therapy is effective and safe, unnecessary operation can be avoided or less extensive procedure such as minimally invasive endoscopic surgery may be applied.
In assessing the effectiveness of PEI therapy in AFTN, previous studies showed excellent results as much as 50–90% by defining response as normalization of thyroid hormone level and recovery of extranodular uptake [15–19]. However, considering that AFTN is a monoclonal neoplasm, an indispensable component to interpret the response of PEI therapy would be whether or not the hot nodule itself disappears after PEI therapy.

In this study, we describe our long-term follow-up experience of PEI therapy in 198 benign solid nodules, 432 benign complex cysts and 24 AFTN patients. The aim of this study was to clarify the long-term efficacy and safety of PEI therapy in benign nodular and cystic thyroid diseases, and to evaluate the response by criteria defined as disappearance of hot nodule after PEI therapy.

Subjects and Methods

Subjects

The study protocol was designed according to the Declaration of Helsinki. All patients were enrolled after obtaining their signed informed consent. From September 1995 to September 2000, we finally recruited a total of 654 patients, 592 (90.5%) women and 62 (9.5%) men with mean age of 42 years (range 15–76 years), who were diagnosed as benign thyroid solid nodule, benign thyroid complex cyst and AFTN based on the following criteria.

(1) Solid nodule and complex cyst groups: In solid nodule group, 198 patients were evaluated by thyroid ultrasound (US), $^{99m}$TcO4 thyroid scan and fine needle aspiration cytology (FNA) under thyroid US guidance, which demonstrated homogenous echogenicity, cold nodule and benign cytology, respectively. Cases that had microcalcification or incomplete capsule formation in thyroid US were excluded. All patients in this group were divided into two subgroups according to initial volume (volume before the first session of PEI therapy): the one subgroup (n = 69) had initial volume more than 10 mL; the other subgroup (n = 129) had initial volume less than 10 mL.

In complex cyst group, 432 patients demonstrated mixed echogenicity, cold nodule and benign cytology in thyroid US, $^{99m}$TcO4 thyroid scan and FNA, respectively. According to initial volume (volume before the first session of PEI therapy), this group was categorized as follows: the one subgroup (n = 161) had initial volume more than 10 mL; the other subgroup (n = 271) had initial volume less than 10 mL.

In both groups, total T3, free T4 and TSH levels before PEI therapy were within normal range. $^{99m}$TcO4 thyroid scan and thyroid function test before the first session of PEI therapy, and FNA before every session of PEI therapy were performed.

(2) AFTN group: 24 patients were chosen from cases with thyroid nodule that was reported as single hot nodule with suppressed extranodular uptake on $^{99m}$TcO4 thyroid scan. All patients refused radioactive iodine ablation or surgery. When extranodular uptake was not completely suppressed on $^{99m}$TcO4 thyroid scan, we confirmed the autonomy of hot nodule by performing $^{123}$I thyroid scan after administering 100 µg triiodothyronine daily for two weeks. All patients had low TSH levels below normal range. $^{99m}$TcO4 thyroid scan, thyroid function test and FNA for excluding malignancy were performed before every session of PEI therapy. We classified AFTN into two subgroups according to thyroid hormone levels: pre-toxic subgroup (n = 20), total T3 and free T4 are in normal range; toxic subgroup (n = 4), total T3 or free T4 is above normal range. Additive medical or surgical treatment including propylthiouracil or methimazole during PEI therapy and follow-up period was not executed.

Thyroid scan, thyroid function test and FNA

In $^{99m}$TcO4 thyroid scan, we obtained thyroid images by Orbiter camera and ICON computer at 10 minutes after the administration of $^{99m}$TcO4 185 mBq. Total T3 was measured with RIA-mat T3 Kit (Byk-Sangtec Diagnostica GmbH, Germany) by radioimmunoassay (RIA), free T4 using Immunotech Kit (Immunotech, France) by RIA, TSH using SPAC-S TSH Kit (Daiichi, Japan) by immunoradiometric assay (IRMA). The normal ranges are as follows: total T3 60–175 ng/dL; free T4 0.8–1.9 ng/dL; TSH 0.4–5.0 µIU/mL. FNA was performed on each nodule or cyst, and cytologic diagnosis was obtained by independently working two experienced pathologists.

Volume measurement of nodule or cyst

After long axis, short axis and depth of nodule or cyst were measured using 10 MHz linear probe of HDI
3000 scanner (Advanced Technology Laboratories, Bothell, WA, USA), volume was calculated by Formula 1 on the assumption that nodule or cyst would be in the form of an ellipsoid [20]. When the three values were not available, Formula 2 was applied to calculate a supposedly spherical volume [20].

Formula 1:

\[
\text{Volume of ellipsoid (mL)} = \text{long axis (cm) } \times \text{short axis (cm) } \times \text{depth (cm) } \times 0.52
\]

Formula 2:

\[
\text{Volume of sphere (mL)} = \left[\frac{\text{semi-diameter of long axis (cm)}}{2}\right]^3 \times 4.19
\]

In the case of complex cyst, volume was measured before aspiration of cystic fluid. Intra-observer and inter-observer variation coefficients of thyroid US were 3.4% and 4.1%, respectively.

**PEI procedure**

A 23-gauge needle was inserted into nodule or cyst and then 99.9% sterile ethanol (approximately 2–5 mL/min) (Duksan Chemicals, Seoul, Korea) was slowly injected into nodule or cyst under thyroid US guidance without local anesthesia. In solid nodule and AFTN, maximal amount of ethanol instilled into nodule at one session never exceeded 20% of the aspirated volume. In complex cyst, cystic fluids were completely removed, and ethanol was injected into cavity to a volume of 40–100% of the aspirated volume. Ethanol was aspirated again after 2 minutes. Ethanol diffusion through nodule or cyst was monitored as intense echogenicity in real-time observation at thyroid US during PEI procedure. Ethanol injection was stopped if ethanol was fully perfused or patient complained of cervical pain. PEI therapy was performed at 2 month intervals, and was completed when nodule or cyst became a small hypoechoic lesion with disappearance of fluid collection. Complications were evaluated in all treated patients.

**Assessment of effectiveness**

(1) Solid nodule and complex cyst

Post-PEI and final volumes were assessed immediately after the last PEI therapy and at the end of follow-up period, respectively. By calculating volume reduction between initial and final volume (Formula 3), complete response (CR) was defined as volume reduction more than 90% (%Δvol ≥90%) with improvement of local compressive symptoms; partial response (PR), as volume reduction at 50–89% (50% ≤ %Δvol < 90%); no response (NR), as volume reduction less than 50% (%Δvol < 50%) or volume expansion.

Formula 3:

\[
\text{Volume reduction (\%)} = \frac{\text{initial volume (mL) } - \text{final volume (mL)} }{\text{initial volume (mL)}} \times 100
\]

(2) AFTN

PEI therapy was defined to be curative only in cases of disappearance of hot nodule with normalization of thyroid hormone level and restored extra-nodular uptake. Persistence of hot nodule regardless of thyroid hormone level or extra-nodular uptake was considered as failure.

**Statistical analysis**

Paired t-test was applied to evaluate changes between initial and post-PEI or final volumes, and between initial and final thyroid hormone levels. Student’s t-test was applied to compare volume reduction between the two subgroups in solid nodule and complex cyst. Pearson’s correlation analysis was applied to evaluate correlations between initial and final volumes, between initial volume and volume reduction, and between mean amount of injected ethanol and volume reduction. Each statistical value was described as mean ± standard deviation (SD). P value less than 0.05 (two-tailed) was considered to be significant.

**Results**

**Effectiveness of PEI therapy in solid nodule and complex cyst**

In solid nodule, 40 (20.2%) patients underwent PEI therapy once, 81 (40.9%) patients two times, 46 (23.3%) patients three times, 20 (10.1%) patients four times, 7 (3.5%) patients five times and 4 (2.0%) patients six times. Mean number of treatment was 2.2 ± 1.4 (median, 2.0), and mean amount of injected ethanol at each session was 2.7 ± 1.4 mL. Follow-up duration after the last PEI therapy was 36.2 ± 13.0 months (Table 1). Initial volume of 15.7 ± 12.2 mL was significantly reduced to post-PEI volume of 2.4 ± 1.7 mL (70.1 ± 14.9% vs. initial volume, p<0.001), and to final volume of 1.8 ± 1.1 mL (75.1 ± 12.3% vs.
Volume reduction during follow-up period persisted after the last PEI therapy (Table 2). CR, PR and NR were 17.2% (34/198), 71.7% (142/198) and 11.1% (22/198), respectively. Volume reduction of the subgroup in which initial volume was 10 mL or more was significantly higher than that of the subgroup in which initial volume was less than 10 mL (85.8 ± 12.3% vs. 62.8 ± 10.7%, p < 0.001).

Although significant correlation was not found between total or mean amount of injected ethanol and volume reduction (p = 0.301, r = 0.269; p = 0.389, r = 0.073), correlations between initial and final volumes (p<0.001, r = 0.411), and between initial volume and volume reduction (p = 0.02, r = 0.495) were significant.

In complex cyst, 67 (15.5%) patients underwent PEI therapy once, 202 (46.8%) patients two times, 108 (25.0%) patients three times, 36 (8.3%) patients four times, 14 (3.2%) patients five times, 3 (0.7%) patients six times and 2 (0.5%) patients seven times. Mean number of treatment was 2.3 ± 1.2 (median, 2.0), and mean amount of injected ethanol at each session was 3.1 ± 2.2 mL. Mean follow-up duration after the last session of PEI therapy was 36.5 ± 12.9 months (Table 1). Initial volume of 15.6 ± 12.6 mL was significantly decreased to post-PEI volume (2.8 ± 2.1 mL, p < 0.001), and to final volume (2.5 ± 1.6 mL, p < 0.001). Volume reduction during follow-up period is summarized in Table 2. Responses at the end of follow-up period were as follows: CR, 19.0% (82/432); PR, 60.4% (261/432); NR, 20.6% (89/432). Volume reduction according to initial volume had a significant difference in two subgroups (≥10 mL vs. <10 mL, 83.4 ± 17.1% vs. 67.6 ± 11.8%, p<0.001). Correlations between initial and final volumes (p<0.001, r = 0.43), and between initial volume and volume reduction (p<0.001, r = 0.47) were significant but no correlation was obtained between total or mean amount of injected ethanol and volume reduction (p = 0.377, r = 0.21; p = 0.398, r = 0.23).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of solid nodule, complex cyst and AFTN groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solid nodule (n = 198)</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>F/U (months)</td>
</tr>
<tr>
<td>Initial vol (mL)*</td>
</tr>
<tr>
<td>Post-PEI vol (mL)†</td>
</tr>
<tr>
<td>Final vol (mL)‡</td>
</tr>
<tr>
<td>%Δvol (%)§</td>
</tr>
</tbody>
</table>

*: the volume before the first session of PEI therapy
†: the volume of the first follow-up period, p<0.001 vs. initial volume
‡: the volume of the last follow-up period, p<0.001 vs. initial volume
§: reduced volume (initial volume – final volume) × 100/initial volume

<table>
<thead>
<tr>
<th>Table 2. Volume changes after PEI therapy in solid nodule, complex cyst and AFTN groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
</tr>
<tr>
<td><strong>Solid nodule (n = 198)</strong></td>
</tr>
<tr>
<td>(mL)</td>
</tr>
<tr>
<td>(%)*</td>
</tr>
<tr>
<td><strong>Complex cyst (n = 432)</strong></td>
</tr>
<tr>
<td>(mL)</td>
</tr>
<tr>
<td>(%)*</td>
</tr>
<tr>
<td><strong>AFTN (n = 24)</strong></td>
</tr>
<tr>
<td>(mL)</td>
</tr>
<tr>
<td>(%)*</td>
</tr>
</tbody>
</table>

*: volume change vs. initial volume
Effectiveness of PEI therapy in AFTN

Two (8.3%) patients underwent PEI therapy once, 11 (45.9%) patients two times, 5 (20.8%) patients three times, 3 (12.5%) patients four times and 3 (12.5%) patients five times. Mean number of treatment was 2.4 ± 1.3 (median, 2.0). Mean amount of injected ethanol at each session was 2.9 ± 2.3 mL. Follow-up duration after the last PEI therapy was 36.7 ± 11.3 months (Table 1). When we analyzed volume reduction during follow-up period although it was not a criterion of effectiveness in this study, initial volume of 11.0 ± 1.9 mL was significantly reduced to post-PEI volume of 1.8 ± 1.5 mL (74.2 ± 15.3% vs. initial volume, p<0.001), and to final volume of 2.0 ± 1.7 mL (71.5 ± 18.0% vs. initial volume, p<0.001) (Table 2). Nineteen (79.2%) patients had volume reduction more than 50% at the end of PEI therapy, and 16 (66.7%) patients obtained persistent volume reduction.

There was significant difference between initial and final TSH levels (0.02 ± 0.01 vs. 0.91 ± 0.18, p = 0.013) but no significant difference was seen between initial and final free T4 levels (1.7 ± 0.4 vs. 1.4 ± 0.5, p = 0.055). Hot nodules on 99mTcO4 thyroid scan persisted in 20 (83.3%) patients, and recurred in 3 (12.5%) patients after transient disappearance through follow-up period. When effectiveness of PEI therapy was assessed by criteria including disappearance of hot nodule, only 1 (4.2%) pre-toxic patient was curative. Reexpanded or recurred AFTN after PEI therapy was observed in 5 patients (2 reexpanded, 2 recurred, 1 reexpanded and recurred). Among 23 patients with persistent or recurred hot nodules, 20 patients had radioactive iodine ablation, and 3 patients were referred for subtotal thyroidectomy.

In 20 pre-toxic patients, volume reduction was greater than 50% in 17 patients at the last PEI therapy, and in 16 patients at the end of follow-up period. Thyroid hormone levels were normalized in 17 patients at the last session of PEI therapy, and in 1 case at the end of follow-up period. Changes of TSH levels (initial vs. final, 0.01 ± 0.01 vs. 0.78 ± 0.61, p = 0.023) and free T4 levels (initial vs. final, 2.5 ± 0.8 vs. 1.9 ± 0.7, p = 0.046) were significant.

Complications of PEI therapy

Complications developed in 41 (9.0%) patients but there was no permanent or serious complication in this study. Transient local pain over injection site, which was the most common complication, occurred in 36 (4 AFTN and 32 complex cyst) patients. Temporary unilateral vocal cord paralysis diagnosed by flexible laryngoscopy occurred in 3 (0.7%) patients but they fully recovered within 2 months. Bleeding at injection site occurred in 1 (0.2%) patient, and transient systemic hypotension, systolic blood pressure was measured less than 90 mmHg, occurred in 1 (0.2%) patient immediately after PEI therapy but was completely normalized within 30 minutes.

Discussion

Ethanol causes complex and irreversible tissue injury such as hemorrhagic infarct, thrombus formation, coagulation necrosis and fibrosis in the central region of injected area. In the periphery, on the other hand, ethanol induces reversible changes by modification of intracellular microstructure and enzymatic activity [21]. Ever PEI therapy in thyroid cyst was performed in 1989 by Rozman et al., it has been increasingly applied as an alternative therapeutic procedure in various benign thyroid diseases [12].

Treatment for benign thyroid solid nodule includes thyroid hormone suppressive therapy and surgery. Although many thyroidologists recommend thyroid hormone suppressive therapy, the efficacy of this option is still unclear because spontaneous regression rate of benign solid nodule is as much as 20–30% [1]. In addition, thyroid hormone suppressive therapy may develop or accelerate atrial fibrillation and osteoporosis especially in elderly patients [1]. Surgery is usually curative but it may be rarely complicated by vocal cord paralysis or hypoparathyroidism. Moreover, surgical and anesthetical risks should be considered. After PEI therapy in benign solid nodule was introduced, preliminary data revealed that the therapy was relatively effective and safe [11, 22, 23]. We also previously reported
the results that repeated PEI therapy in benign solid nodule led to more than 50% volume reduction in all treated patients at 14 months after the end of PEI therapy [24]. Caraccio et al. treated benign cold nodule with combination regimen of thyroid hormone suppressive therapy and PEI therapy, and reported 74.8% volume reduction at 1-year follow-up [22]. In the present study, more than 50% volume reduction only by PEI therapy was achieved in 88.9% (CR 17.2% and PR 71.7%), and mean volume reduction was 72.9% at the end of follow-up period. These results strongly suggest that PEI therapy may be an effective means of treating benign solid nodule. Although no correlation was demonstrated between amount of injected ethanol and volume reduction, the correlations between initial and final volumes, and between initial volume and volume reduction were significant, which suggest that PEI therapy may be more effective in larger nodules. This hypothesis is also supported by the result that volume reduction was significantly higher in cases of initial volume more than 10 mL.

In benign thyroid complex cyst, some investigators reported that more than 50% volume reduction was observed in 72–95% of treated patients by injecting tetracycline or ethanol [25–28]. Prete et al. reported that PEI therapy was effective even in large symptomatic cyst [29]. On the contrary, Hegedus et al. reported that injection therapy had no significant effect on cyst [30]. The present study showed that benign complex cyst was decreased by more than 50% in 79.4% (CR 19.0% and PR 60.4%) of the patients at the end of follow-up period. This means that PEI therapy may be considered as the first choice of treatment in benign complex cyst. Significant correlation between initial volume and volume reduction in this study was consistent with the result by Verde et al., and volume reduction in cases between initial volume more than 10 mL and initial volume less than 10 mL showed significant difference as well [26]. These results are interesting because some authors reported that initial volume was not correlated or inversely correlated with volume reduction in benign complex cyst [19, 31].

The standard strategies for treatment of AFTN are surgical removal or radioactive iodine ablation [5, 6]. However, surgery often has serious peri- or postoperative complications, and radioactive iodine ablation requires special equipment. Since Livraghi et al. first applied PEI therapy to AFTN in 1990, PEI therapy has been proposed as a suitable alternative non-surgical treatment of AFTN, and many data have showed PEI therapy to be effective and safe throughout the short-term follow-up period [13, 15–19, 32–35]. Recently, Guglielmi et al. suggested that small AFTN, particularly if volume is less than 5 mL and extra-nodular uptake is not yet completely suppressed, should be treated by PEI therapy in patients who refuse radioactive iodine ablation [14]. While previous studies reported high responsive rate by defining remission or cure as normalization of thyroid hormone level and restored extra-nodular uptake, a large-scale five-year follow-up study by Monzani et al. showed that complete cure, defined as normal thyroid hormone level and restored extra-nodular uptake, was achieved in 85.5% but hot nodule itself disappeared only in 11.1% of the patients [15]. This result strongly indicates that PEI therapy may not eradicate hot nodule itself regardless of normalization of thyroid hormone level or restored extra-nodular uptake. In fact, restoration of extra-nodular uptake is not always in accord with the disappearance of hot nodule, and whether hot nodule itself disappears or not may be a more valuable criterion to evaluate effectiveness of PEI therapy in AFTN. In this study, volume reduction was 74.2% but disappearance of hot nodule was only in 4.2%. By criteria including disappearance of hot nodule as well as normalization of thyroid hormone level and restored extra-nodular uptake, the cure achieved by PEI therapy was very much lower than the results reported by previous studies. Moreover, reexpanded or recurred hot nodule after PEI therapy was seen in 20.8%, which was in contrast to the data by Monzani et al. [15]. The difference may be caused by follow-up duration and response criteria. In addition, our study (20 pre-toxic and 4 toxic cases) recruited different case numbers from those reported by Monzani et al. (40 pre-toxic and 77 toxic cases) [15]. Another possibility is that complete eradication of AFTN was not achieved by PEI therapy although the injected amounts were calculated by the same formula that was applied to solid nodules. In the present study, the response rate between pre-toxic and toxic subgroups was not compared because the number of cases in the toxic subgroup was too small to be valid but pre-toxic cases had a tendency to better outcome. As a consequence of failure, 3 patients received subtotal thyroidectomy but fibrotic change at injection site was not observed.

PEI therapy is known to be relatively safe in many previous studies. In this study, permanent or serious
complication did not occur but temporary complication was demonstrated in 9.0%, which was lower than 9.0–34.6% of previous data [18, 27, 31]. Transient local pain at injection site (7.9%) by leakage of ethanol into subcutaneous tissue was the most common complication but much less frequent than previous reports [15, 18, 27, 31]. Temporary unilateral vocal cord paralysis occurred in 0.7%, but we might have overlooked a diagnosis in some patients without dysphonia because only patients with voice change were examined by flexible laryngoscopy. Other side effects including hematoma, dyspnea and transient hyperthyroidism have been reported in several studies [27, 36, 37]. Some studies described the uncommon complication of hypothyroidism, which was related to coexistence of thyroid autoantibodies [15].

In the present study, we could not confirm the pathologic findings because all patients were not operated, and this is one of the major limitations of PEI therapy. Although we repeatedly performed FNA before every session of PEI therapy to exclude malignancy as completely as possible, a few of the nodules or cysts might have been follicular carcinoma because it is very difficult to distinguish follicular adenoma and follicular carcinoma by FNA alone. The consequence of follicular carcinoma after PEI therapy has not been reported. If follicular carcinoma is not completely eradicated by PEI therapy, it may recur or even metastasize.

In conclusion, these results suggest that PEI therapy could be an effective and safe treatment for benign nodular and cystic thyroid diseases especially when initial volume is more than 10 mL, but may not cure hot nodule itself in AFTN.

Acknowledgement

This work was supported by the Research Grant (to S. J. Lee) from Hallym University, ChunCheon, South Korea.

References

17. Papini E, Panunzi C, Pacella CM, Bizzarri G, Fabbri


