Turkish Journal of Endocrinology and Metabolism, (2000) 1 : 27-31 **ORIGINAL ARTICLE**

Percutaneous Ethanol Injection in Thyroid Nodules: Preliminary Results

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Percutaneous ethanol injection is a new and alternative method for treatment of thyroid nodules. In this study, the feasibility of percutaneous ethanol injection was examined on two types of thyroid nodules. In an autonomously funtcioning thyroid nodule, percutaneous ethanol injection treatment was able to 1) Normalize the suppressed TSH level, 2) Stop autonomous function of the nodule, 3) Restore thyroid activity in the rest of the gland, 4) Diminish the size of the nodule and, 5) Alleviate symptoms. Percutaneous ethanol injection also relieved pressure symptoms and decreased the size of a thyroid cystic nodule. The procedure was well tolerated by the patients. Pain at injection site was the only side effect. According to our initial impression, percutaneous ethanol injection treatment appears to be an effective and safe procedure. Therefore, it should be evaluated in larger series with longer follow-up in our contry.

Key words: Thyroid nodule, percutaneous ethanol injection

Introduction

Percutaneous ethanol injection (PEI) was first introduced for treatment of thyroid nodules in 1990 (1). The procedure has previously been used for treatment of several benign and malignant conditions, including parathyroid and hepatic tumors (2). Özdemir and co-workers were the first researchers who performed PEI in Turkey with successful results (3). This paper reports our center's initial experience with PEI and highlights differences in clinical evolution, technique and outcome for PEI treatment in autonomously functioning thyroid nodules (AFTN) and thyroid cystic nodules (TCN).

Materials and Method

Subject 1: A 57-year-old Turkish woman presented with palpitations and three kilograms of weight loss. Physical examination showed that she had a right thyroid nodule. A complete cardiac work-up including an exercise EKG and Holter monitor was within normal limits. Her thyroid function tests showed that her T_4 level was 8.1 µg/dl (normal range: 5.1-14.1), T_3 level was 129 ng/dl (normal range: 80-200), and TSH level was 0.029 µIU/ml (normal range: 0.27-4.20). Thyroid ultrasonography showed a 15.7x14.4x16.2 mm hypoechoic solid nodule in the right and two smaller nodules (6.7x4x8.4 and 3.6x2.5x3.4 mm) in the left thyroid lobe. Technetium-99m thyroid scan showed that the right nodule was hyperactive and the left nodules were hypoactive with a decreased uptake in the rest of the gland.

The patient had subclinical hyperthyroidism from a right hyperactive nodule in a multinodular goiter. A DEXA bone mineral density study showed that her T score was-0.78 at femoral neck and +0.51 at L2-L3 spine level. The patient refused surgical intervention and radioiodine administration. PEI was instituted. Initially, fine needle aspiration of the right thyroid nodule was performed. There were no malignant cells. A total dose of 8ml sterile 95% ethanol was injected in four sessions under real time ultrasound guidance. There were no side effects.

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Follow-up thyroid scintiscan done 6 months after PEI showed that the treated nodule was hypoactive rather than hyperactive.

Extranodular radiotracer uptake was restored and left thyroid nodules appeared normoactive in this scan. The patient's palpitations were resolved and a gradual increase of TSH to normal range was observed during this time. Fifteen months after PEI, her T4 (6.6 µg/dl) and T3 (104 ng/dl) levels were similar to baseline, though her TSH level rose to 0.38 µIU ml. Twenty-two months after PEI, her TSH level (0.33µIU/ml) was still normal. Thyroid ultrasonography done at that time showed a 10.6x7.6x5.1 mm hypoechoic nodule in the right lobe and two left side nodules with unchanged size (5.7x4.9x8.5 and 3.5x2x3.3mm).

Subject 2 : A 36-year-old man presented with sudden onset of pain in the left side of his neck, associated with low-grade fever and malaise. Physical examination revealed a large, tender, soft thyroid nodule in the left lobe. Complete blood cell count, erythrocyte sedimentation rate and TSH (1.24 µIU/ml, reference range: 0.27-4.20) were within normal limits. Thyroid scan showed a large cold area in the left lobe. Ultrasound examination showed a large hypoechoic mass measuring 34x28x27 mm in the left lobe. The volume of the cyst was 13 ml and was calculated according to ellipsoid formula (4). Fine needle aspiration biopsy of the cyst showed abundant colloid with no malignant cells. Complete evacuation was documented by ultrasound. The cyst recurred one week later, with the same dimensions. One month later, a second fine needle aspiration was performed. Repeat cytology showed no malignant features. Surgery was recommended for recurrent symptomatic thyroid cystic nodule, but was refused by the patient. After complete aspiration of the cyst, 2 ml sterile 95% ethanol was injected under real-time ultrasound control. The patient complained of moderate pain during the injection. One month later the cyst measured 23x13x20 mm on ultrasound examination with a post-treatment volume of 3.1 ml.

PEI Technique : Before starting the procedure one must first exclude the rare possibility of thyroid malignancy in hyperactive thyroid nodules. A total dose of 1 to 1.5 ml of 95% sterile ethanol per mililiter of nodular volume is injected slowly via 20-22 gauge needle under real time ultrasound guidance. The total dose should be divided into two to twelve, on average four weekly sessions and the amount per each injection should range between 1 to 8 ml (5, 6). We monitored the injection as a hyperechogenic region and completed the procedure in five minutes. After a successful PEI procedure, color Doppler examination shows complete disappearance of intranodular hypervascularization (7, 8). In nodules located near the posterior region of the gland, one should be careful to avoid ethanol spillage near the recurrent laryngeal nerve. Otherwise, dysphonia due to transient laryngeal nerve palsy will occur. In the following weekly perfusions, ethanol should be injected into untreated areas of the nodule (6).

The technique for treating thyroid cystic nodules differs in ethanol dose and number of sessions (2,9). It is imperative to obtain fine needle aspiration biopsies from the solid components, as these areas may habour foci of papillary carcinoma. If there is any suspicion of malignancy, surgery must be performed. Simple aspiration may cure the cyst in 20 to 90 % of patients (2). If the cyst accumulates fluid, then PEI should be considered. Sterile ethanol should be injected slowly in an amount of 10 % of the nodular volume under real time ultrasound guidance (2). We followed another protocol that recommended delivering 2 ml ethanol for TCNs less than 20 ml in size (9).

Results and Discussion

Radioactive iodine and surgery are two well-established options for the management of autonomously functioning thyroid nodules. The success rate of radioiodine ranges from 83 to 90 % according to the size of the nodule and administered dose (10). Radioiodine use is controversial in young women. Its major drawback is late hypothyroidism, which is reported in between 0-36 % of patients after I^{131}therapy for AFTNs (11). The average rate of hypothyroidism is 15 % after radioactive iodine treatment. Surgery is recommended in large (>3 cm) hyperactive nodules (10). Complications are rare in experienced hands and short-term

success rates approach 100 %. Its disadvantage lies in its high cost and some patients do have contraindications to surgery. Hypoparathyroidism (0-3.6 %) and vocal cord damage (0-4.4 %) are the main side effects of surgery. Although hypothyroidism is observed on average at a rate of 12 % after surgery, studies with longer follow-up extending to nine years report its occurrence as 41 % (10,12). Surgery and radioiodine have different success rates and different side effect profiles. One must consider the pros and cons of these modalities when recommending them to patients.

PEI is a new and alternative treatment method. So far studies involving more than 500 subjects from Europe, Turkey and Japan have been published (1-3,5-9,13,14). An Italian multicenter study (6) reports successful results in 66.5 % of toxic adenomas and 83.4 % of pretoxic adenomas for a duration of 12 months follow-up. The investigators correlate cure rates with the size and function of the AFTNs. They achieved 90-100 % complete cure rate in nodules smaller than 15 ml (6). Özdemir and co-workers studied PEI on 16 subjects with an AFTN. Fifteen patients had a complete cure and one patient had a partial cure. Thyroid hormone levels and TSH returned to normal in all treated patients (3).

The management of pretoxic AFTNs is still debated, because only 10 % of pretoxic nodules progress to overt hyperthyroidism (15). Therefore, some authors propose a wait-and-see strategy. However, early treatment is advised in elderly patients with arrhythmia, cardiac failure or osteoporosis (10). Therapy was indicated in subject-1 because of palpitations. She did not have osteoporosis. In pretoxic nodules that are less than 3 cm in diameter, the possibility of toxic evolution is no more than 20 % in six years (15). Although our patient could have been followed with beta-blocker treatment, PEI was instituted to correct her suppressed TSH level and symptoms. In addition to its favourable results, PEI has the advantage of not affecting extranodular thyroid tissue. I^{131} therapy causes significant radiation exposure to extranodular thyroid tissue and has been associated with hypothyroidism (10,11). This is especially true in pretoxic nodules. These beneficial outcomes justify PEI as a prophylactic approach for pretoxic nodules to prevent their toxic evolution (7).

In the first subject, the hyperactive nodule appeared cold six months after PEI. As follicular cells are damaged by ethanol, they neither accumulate radioiodine nor secrete excess thyroid hormones. Therefore, the treated nodule appears hypoactive in scintiscan. Up to date, FNA biopsies of cold nodules resulting from PEI have not revealed any evidence of malignancy (2, 5, 7, 14). In the Italian multicenter study 55 % of toxic adenomas and 65 % of pretoxic adenomas appeared cold in thyroid scintiscan performed one year after PEI (6).

Six months after PEI treatment, the extranodular thyroid tissue was able to concentrate radiotracer in subject-1. This is another beneficial aspect of PEI. In several studies, functional activity of previously suppressed extranodular thyroid tissue was recovered in 71-86 % of patients (5-7). The rate of recovery was higher in pretoxic (80 %) than toxic (61.5 %) nodules. PEI restores extranodular thyroid function in equivalent rates as radioiodine (11).

The ability of PEI to reduce nodular volume was impressive in subject-1. The pre-treatment nodule volume was 1.9 ml, whereas it was 0.2 ml two years after PEI. The nodule appeared more hypoechoic with loss of solid parts in the last ultrasonography. Marked nodule volume reduction, by about 75-95 %, was observed in all patients treated by PEI (5-7, 13, 14). The nodule size was decreased in 81 % of subjects treated by PEI in a paper from Gazi University Schooll of Medicine (3).

The second subject had a large thyroid cystic nodule and his symptoms were probably related to a recent bleeding inside the cyst. He refused surgery and PEI was performed. Although follow-up time is short, volume reduction is remarkable in this case. PEI is reported to be a safe, effective and probably definitive mode of treatment for thyroid cystic nodules (2). The treated nodule should be a pure cyst and should not contain any solid parts or septations which may contain malignant cells. Zingrillo and co-workers (9) followed 43 PEI-treated cysts for five years. In 93 % of the patients, a significant nodule volume reduction (92 %) was observed, accompanied by an improvement in symptoms and tracheal displacement. PEI failed only in 7 % of patients. All the failed subjects had large cysts over 50 ml (9).

Mechanism of PEI: The therapeutic effect of ethanol is attributable to its diffusion into the cells and to its

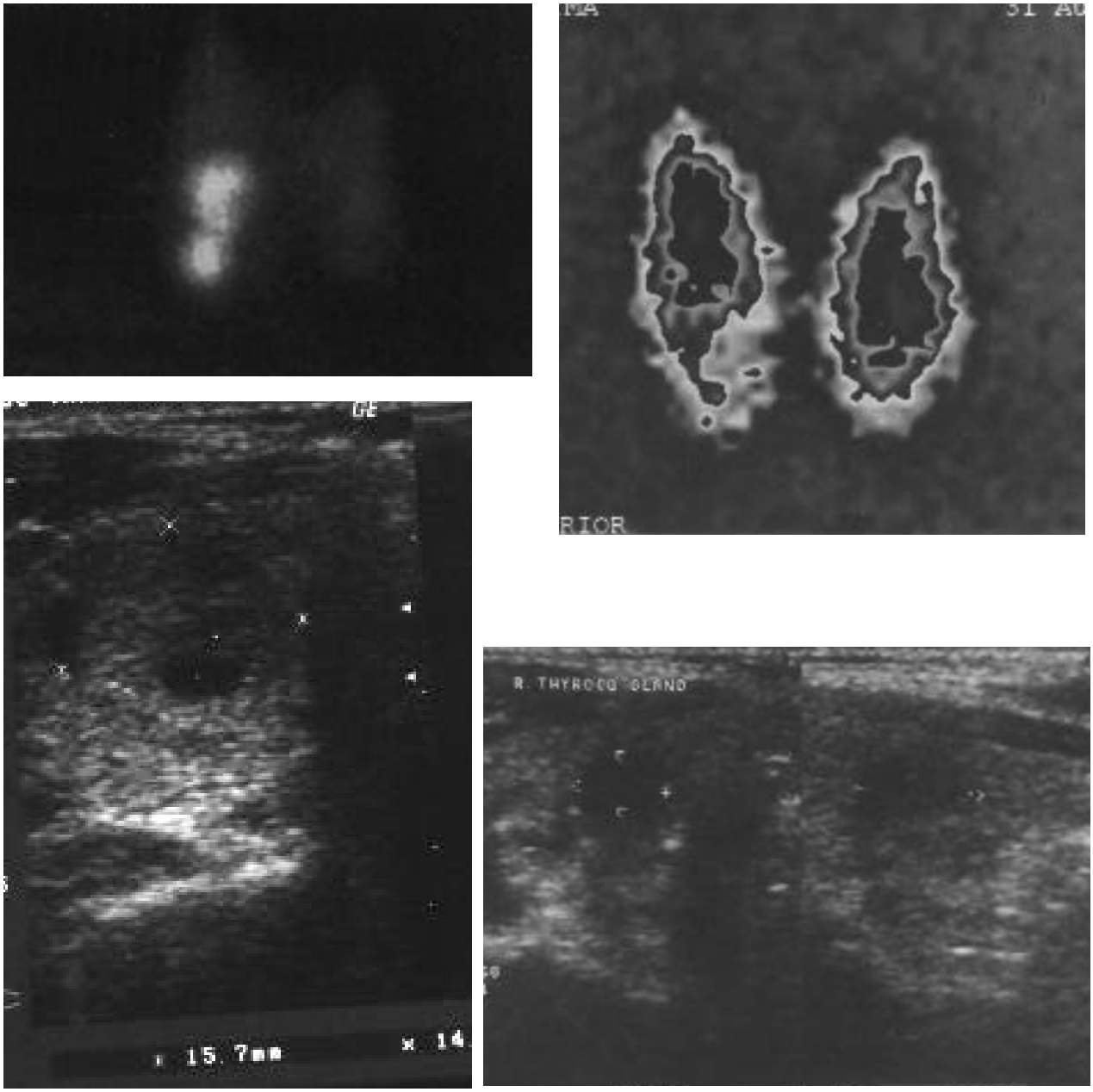

Figure 1.

A- Thyroid scan before PEI shows a hyperactive right thyroid nodule with diminished extranodular activity.
B- Six months after PEI, the nodule appears cold with restored extranodular thyroid uptake.
C- Thyroid ultrasonography in a thyroid cystic nodule shows a large tyroid cyst (34x28 mm) before PEI.
D- The cyst is aspirated and ethanol is injected. Ethanol is observed as a hyperechogenic area immediately after injection.

distribution in high concentration into the local vascular supply. Ethanol directly causes thyroid follicular cell necrosis due to cell dehydration and protein denaturation (2). The vascular distribution of ethanol causes indirect damage, first dehydration of the endothelium and blood cells, then thrombus formation and subsequent tissue ischemia with hemorrhagic infarction. This is followed by fibrotic changes (16). Fine needle aspiration biopsies of nodules treated by ethanol show necrotic material consisting of histiocytes, few follicular cells and colloid (5, 6, 16).

Side Effects : PEI is a well-tolerated procedure (5-9, 14). A burning sensation during the injection is usually felt (3). Pain radiates to the jaw or retroauricular area

in 30 % of the patients. Other side effects (6) are fever lasting a day (8 %), transient dysphonia (3.9 %), hematoma (3.9 %) and jugular vein thrombosis (0.23 %). A nearly but transient increase in serum levels of thyroid hormones results from abrupt release of stored thyroid hormones following follicular disruption produced by ethanol. This is of no clinical significance in pretoxic nodules, because free thyroid hormonle levels are always within the normal range. Toxic patients may have moderate aggravation of symptoms. Free T_3, and free T_4 valuess how a modest increase during the first 24 hours after PEI. Overtly hyperthyroid patients with cardiac problems are in need of rapid relief of thyrotoxicosis. PEI requires two to four weekly sessions to restore euthyroidism. Therefore, the slow onset of effect is a disadvantage of the method in patients with cardiac disease. This is also true for patients who develop antithyroid drug toxicity. Nevertheless, PEI was a very well tolerated procedure in our patients.

Conclusions: PEI was successful in normalizing TSH level, decreasing the nodular size and restoring extranodular uptake in the first subject who had an autonomously functioning thyroid nodule. PEI decreased the size of the thyroid cyst in the second subject and improved his symptoms. Moderate pain during the injection was the only side effect. According to our initial experience, PEI appears to bea safe and effective technique. It is worthwhile to evaluate its performance in a large series with longer follow-up.

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