Turkish Journal of Endocrinology and Metabolism, (2003) 3 : 113-118 **ORIGINAL ARTICLE**

Ethanol Injection as a Treatment Modality in Autonomous Thyroid Nodules: 2 Years Follow-Up

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Recently, percutaneous ethanol injection therapy (PEIT) has been used as an alternative to surgery and radioiodine for the management of autonomously functioning thyroid nodules. Here we report our experience on the efficacy and complications of PEIT on toxic thyroid nodules in two years follow-up.

In 26 patients with autonomously functioning thyroid nodules, the levels of free triiodothyronine (FT_3), free thyroxine (FT_4), and thyrotropin (TSH), ultrasound and scintigraphic evaluation of thyroid gland before, 6 and 24 months after ethanol injection were determined. PEIT was performed after excluding malignancy by fine-needle aspiration biopsy. Each patient underwent 3-8 sessions (mean 4 ± 1) of PEIT, with an injection of 1.5-8.0 (mean 3.76 ± 1.67) mL total amount of ethanol. Results: Mean nodule volume reduced from 5.5 ± 6.1mL to 2.8 ± 3.8mL 6 months after therapy (p=0.0001) and to 2.6 ± 4.1mL (p=0.001) 24 months after therapy at ultrasound evaluation. Nodule volumes showed a significant shrinkage 6 and 24 months after therapy (92.3% and 90.0%, respectively). During follow-up, hyperfunctioning nodule became cold in 11 (42.3%) and relatively active in 7 (26.9%) of patients at scintigraphy. TSH levels increased to normal levels in 17 (65.4%), and persisted below normal levels in 9 (34.6%) patients. Injections were well tolerated by all patients. Treatment did not cause considerable side effects.

PEIT can be considered as practical, effective and cost-effective treatment as an alternative method to surgery and radioiodine without any severe complication particularly hypothyroidism for benign toxic nodules.

Key words: Thyroid nodules, ethanol injection, treatment

Introduction

The established treatment modalities for the patients with toxic nodular thyroid disease are surgery or radioiodine therapy. Despite their good results, these treatments may lead to some complications such as injury of the recurrent laryngeal nerve or hypoparathyroidism after surgery and late hypothyroidism which has a prevalence as high as 36-45% from 5 to 20 years after radioiodine therapy and 22% after surgery (1-3). Ultrasound-guided percutaneous ethanol injection therapy (PEIT), which is considered more safe and as effective as other modalities, has recently been proposed as an alternative to the standard therapies for the management of autonomously functioning thyroid nodules and parathyroid lesions in selected patients (4,5).

This method is increasingly used for the last 5 years. In the present study we aimed to evaluate the efficacy and safety of PEIT on patients with toxic thyroid nodules who were followed up to 2 years.

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Materials and Methods

26 patients (17 females and 9 males; mean age 47.3 ± 10.9 years, range 30-73) were included in

the study. Sixteen patients (61.5%) had toxic solitary nodules and 10 (38.5%) had toxic non-solitary but dominant nodules. Malignancy was excluded in all patients by fine-needle aspiration biopsies. All patients were evaluated before and 6 and 24 months therapy, and measurements included serum thyrotropin (TSH), free thyroxin (FT_4), free triiodothyronine (FT_3), thyroglobulin (Tg), thyroglobulin and the thyroid peroxidase (TPO) antibodies by radioimmunoassay method. Thyroid ultrasound examination was performed immediately before ethanol injection and then repeated 6 and 24 months after procedure. The nodule volumes were calculated using the formula width × length × anteroposterior diameter × 1/6 π (6) for spheres or ellipsoids. (99m Te-pertechnetate) thyroid scintiscan was performed before and after 6 and 24 months of the treatment. All patients were informed about the ethanol treatment and their consents were obtained. Sterile ethanol 95% was injected 3-8 sessions (mean 4 ± 1) without local anesthesia under ultrasound control by the same specialist in the outpatient department. Alcohol was administrated once weekly as a single injection per session. Amount of ethanol injected into the nodule (in each session) was decided in regards of the nodule volume. About 1.5 to 8.0mL (mean 3.76 ± 1.67) total amount of ethanol was injected during the treatment.

Complete cure was defined as reaching to the normal levels of serum FT_3, FT_4, TSH, no clinical evidence of thyrotoxicosis and hypoactive nodule in thyroid scintiscan. Partial cure was defined as having normal levels of FT_3, FT_4 and detectable serum TSH, remission of clinical evidence of thyrotoxicosis and toxic nodules with partially reacted extranodular tissue. No response was defined as no clinical, biochemical and scintigraphic change.

Statistical analysis was done with the SPSS PC (+) statistical package. Comparisons of non-quantitative variables in dependent groups were performed with Wilcoxon test for 2 groups and Friedman test for 3 groups (thyroid gland, nodule volume and thyroid hormone). When a significant difference was found in 3 dependent groups, Signed Ranks analysis was used with Bonferroni correction (TSH levels before and 6, 24 months after treatment). χ^2 test was used for quantitative variables (nodule volume and response). Kruskal Wallis analyses of variance was used for the comparison of non-quantitative variables in 3 independent groups (clinical status and shrinkage in nodule volume). Spearman correlation analysis was carried out to evaluate the relationship between volume reduction and other parameters. All data are presented as means ± SD. P values < 0.05 were considered statistically significant.

Results

Table 1 shows some of the clinical characteristics of the patients. The procedure was technically successful in all cases. The treatment was well tolerated by all patients. All patients completed the study. Thyroid fine needle aspiration was repeated in 2(7.7%) patients who had increased nodule volume at the 6 month of therapy. These patients underwent one to three additional ethanol injections.

Table 1. Clinical characteristics, laboratory findings and serologic data of the patients

Sex (M/F)	9/17
Age (Year)	47.3 ± 10.9
Size	
Nodule volume (mL)	5.50 ± 6.16 (0.24 - 23.89)
Perinodular thyroid volume (mL)	21.3 ± 18.33 (8.31 - 66.22)
Morphology (no.)	
Purely solid	19
Solid with cystic spaces	7
Predominantly cystic	0
Number (no.)	
Single nodule	16
Multinodule	10
History of thyroidectomy (no.)	0

Table 2 summarizes the outcome of PEIT. In the ultrasound evaluation, pretreatment thyroid gland volume decreased from 28.7 ± 18.3 mL to 21.7 ± 13.9 mL after PEIT (p=0.009). A significant reduction in the nodule volume was observed in 24 (92.3%) and 18 (90%) patients at 6 month and 24 month of the therapy respectively. Mean pretreatment nodule volume decreased to from 5.50 ± 6.16 to 2.8 ± 3.8 mL at the 6 month of therapy ($p<0.0001$) and to 2.6 ± 4.1mL at the 24 months of therapy (p=0.001). A 49% reduction at 6 month and 52% at 24 month of therapy were observed in nodular volume. Nodular shrinkage was strongly correlated with the amount of ethanol (r=0.461, p=0.018) and number of injections (r=0.522, p=0.006). It did not correlate with the patient's pretreatment situation including euthyroidism, subclinical hyperthyroidism and hyperthyroidism ($p>0.05$).

Table 2. Treatment outcome in patients after percutaneous ethanol injection.

PT no.	Scintigraphy		Nodule volume (mL)			Before treatment			After treatment					
	Before	After	Before	6.m	24.m	T_3	T_4	TSH	6. m			24.m		
									T_3	T_4	TSH	T_3	T_4	TSH
1.	active	relatively active	2.09	10.41	5.64	3.0	1.0	0.74	2.58	1.0	0.55	2.50	1.60	0.35
2.	active	hypoactive	3.76	1.19	0.67	3.53	1.28	0.15	3.51	1.81	0.28	3.52	1.27	0.34
3.	active	hypoactive	4.04	2.09	2.24	3.52	1.71	0.03	3.51	1.72	1.02	3.49	1.69	1.01
4.	active	active	4.50	1.34	1.37	3.10	2.0	1.31	3.01	2.10	2.60	3.20	2.20	2.50
5.	active	relatively active	11.93	2.92	2.92	6.50	1.70	0.03	3.60	1.50	0.81	2.60	1.0	0.29
6.	active	active	15.16	0.72	0.88	7.70	3.10	0.01	2.90	0.58	0.20	2.80	0.59	0.01
7.	active	hypoactive	0.54	0.03	0.05	2.55	1.54	0.04	3.21	1.30	0.05	2.08	1.24	0.06
8.	active	relatively active	1.09	0.98	0.80	3.50	1.17	1.74	3.90	1.60	0.64	3.80	1.70	0.65
9.	active	hypoactive	1.04	0.28	0.17	3.60	2.0	0.01	2.40	0.91	2.60	2.50	0.92	2.60
10.	active	relatively active	8.32	6.24	6.22	2.55	1.54	0.58	2.56	1.55	1.05	2.57	1.54	1.02
11.	active	hypoactive	0.24	0.04	0.04	2.58	1.64	1.79	2.68	3.73	1.80	1.41	1.37	1.86
12.	active	active	3.43	2.39	3.70	2.80	0.97	3.06	3.48	1.27	0.34	3.47	1.28	0.34
13.	active	relatively active	1.98	0.54	0.55	2.70	0.90	0.03	2.60	1.60	0.43	3.10	0.96	0.60
14.	active	active	8.71	4.77	4.50	4.50	1.20	0.02	5.70	1.30	1.23	5.60	1.40	1.22
15.	active	relatively active	10.09	3.29	2.20	4.03	1.30	0.01	3.46	1.14	0.03	3.12	1.54	1.18
16.	active	hypoactive	2.46	0.33	0.0	3.60	1.40	3.50	3.0	1.30	0.60	2.70	1.0	0.91
17.	active	hypoactive	1.04	0.0	0.0	2.88	1.11	0.62	3.10	1.12	2.20	2.98	1.13	2.40
18.	active	active	2.39	3.74	1.37	5.47	1.59	0.01	3.48	1.08	0.21	3.20	0.87	0.16
19.	active	hypoactive	8.52	3.70	2.50	2.95	1.13	0.25	2.90	1.40	0.43	2.80	1.20	0.42
20.	active	active	23.89	13.17	12.49	7.78	2.70	0.04	6.24	2.26	0.01	6.19	2.72	0.01
21.	active	hypoactive	0.75	0.20	0.17	3.54	2.21	0.01	2.14	1.44	0.03	3.12	1.24	0.45
22.	active	hypoactive	2.39	1.32	0.04	2.49	1.13	0.66	2.82	1.01	1.04	2.70	1.02	1.02
23.	active	hypoactive	3.71	0.46	3.31	3.09	1.85	0.43	3.18	1.28	3.45	2.98	1.50	3.18
24.	active	active	1.24	0.33	0.62	4.26	1.41	0.13	2.55	1.15	0.03	2.96	1.26	0.13
25.	active	relatively active	0.72	0.62	0.62	1.53	1.45	0.16	1.52	1.42	0.35	1.49	1.43	0.58
26.	active	hypoactive	19.21	12.89	15.41	4.39	1.36	0.01	2.18	0.77	0.03	2.64	0.94	0.65
Total			5.5±6.1	2.8±3.8	2.6±4.1	3.5±1.7	1.6±0.6	0.5±0.9	3.1±1.0	1.4±0.6	0.7±0.7	3.0±1.0	1.3±0.4	0.8±0.7

FT_3, normal range: 2 - 4.2 pg/ml; FT_4, normal range: 0.8 – 1.7 ng/dl; TSH, normal range: 0.35 – 5 uIu/ml

Table 3. Side effects in patients submitted to PEIT

	Patients n (%)
Pain and burning sensation	6 (23)
Transient facial hypoesthesia	1 (3.8)
Transient dysphonia	1 (3.8)
Hematoma	0 (0)
Jugular vein thrombosis	0 (0)

Scintigraphic results showed that nodule activity decreased in 18 (69.2%) patients 24 months after treatment. In 11 (42.3%) patients, toxic nodule became cold and scintigraphic reactivation of extranodular tissue was observed and in 7 (26.9%) patients toxic nodule did not become purely cold but partial reactivation of extranodular tissue was observed. When patients were divided into 3 groups including euthyroid, subclinical hyperthyroid and hyperthyroid according to their pretreatment status, nodules returned to hypoactive scintigraphically in 5 out of 10 (50%) patients in euthyroid group; 5 out of 11 (45.5%) in subclinical hyperthyroid group; 1 out of 5 (20%) in hyperthyroid group scintigraphically. Scintigraphic results also showed that nodule activity decreased to the level of relatively active in 4 out of 10 (40%) patients in euthyroid group; 2 out of 11 (18.2%) in subclinical hyperthyroid group; 1 out of 5 (20%) in hyperthyroid group.

Complete cure was attained in 10 (38.5%) patients, partial cure in 11 (42.3%) patients and no response in 5 (19.2%). With respect to clinical and biochemical remission, number of euthyroid cases increased from 10 (38.5%) to 18 (69.2%), subclinical hyperthyroid cases decreased from 11 (42.3%) to 7 (26.9%) and hyperthyroid cases decreased from 5 (19.2%) to 1 (3.8%) after PEIT. The cure rates did not correlate with the amount of ethanol, number of injections and pretreatment situation ($p>0.05$).

Response to PEIT was found similar in patients with single nodule or with multinodular goiter ($p>0.05$). PEIT was successful in 12 out of 16 (75%) patients with single nodule and in 9 out of 10 (90%) patients with multinodular goiter with respect to response. No difference was observed between solid or mixed nodules ($p>0.05$).

TSH levels rose to normal levels in 18 (69.2%) patients and in 8 (30.8%) patients TSH levels persisted below normal after PEIT. There was a significant difference in mean TSH levels of patients at the 6 and 24 month of therapy ($p=0.011$).

Clinically euthyroidism was observed in all 10 (100%) euthyroid patients; 7 out of 11 (63.7%) in subclinic hyperthyroid group; 1 out of 5 (20%) in hyperthyroid group after treatment. 19 (73.1%) patients did not need to have antithyroid medication until PEIT. 5 (19.2%) patients with hyperthyroidism were treated with propylthiouracil (100-300 mg daily) and propranolol (40-60mg daily), 2 (7.7%) patients only propranolol until they had normal levels of FT_3 and FT_4. The number of the patients who needed medical treatment decreased from 7 (26.9%) to 4 (15.3%) after PEIT.

Clinical and scintigraphic remission did not change during follow-up. One patient (3.8%) who had normal FT_3 and FT_4 levels but persistent scintigraphic nodule activity and progression in the nodule volume, two patients (7.7%) who had no clinical, biochemical and scintigrafic remission of hyperthyroidism were treated by surgery after follow-up period.

Before PEIT, high serum AbTPO and AbTg autoantibody levels were found in 2 (7.7%) cases. These antibodies did not increase after PEIT. Tg increased in 5 (19.2%) patients just after PEIT but returned to normal during follow-up period.

As shown in table 3, side effects included local or radiated pain and burning sensation in 6 (23%) patients; transient facial hypoesthesia in one case (3.8%) was observed. A transient dysphonia lasting one hour was seen in one patient (3.8%) and it resolved without any therapy. Local hematoma or jugular vein thrombosis was not observed during PEIT.

Discussion

Medical treatment such as antithyroid and beta-blocker agents is purely symptomatic and should be continued for along time, may be life long. Surgery or radioiodine therapy may cause severe permanent complications in the treatment of toxic thyroid nodules. Therefore, PEIT has been suggested as an alternative therapy to the classical methods for autonomously functioning nodules.

Once injected in a tissue, alcohol is distributed by diffusion and induces cellular dehydration and protein denaturation, followed by coagulation necrosis, small vessel thrombosis and reactive fibrosis (7). Necrosis and fibrosis cause shrinkage of nodule volume. In accordance with the study of Lippi et al. reporting shrinkage in 85% of patients 12 months after PEIT (8), in our study ultrasonographic outcomes showed a striking nodular volume reduction in 92.3% of patients 6 months after PEIT. It was suggested that decrease of thyroid gland volume after treatment was arised from intranodular fibrosis due to the effect of alcohol injected not a result of ethanol seepage into the extranodular parenchyma.

The effect of pretreatment nodule volume has been discussed since the beginning of PEIT. Although nodule volume is an important factor in predicting the response rate to therapy, there are successful results for both large (>40 mL) most of which are associated with clinical thyrotoxicosis and small (10-15 mL) toxic nodules. For large nodules, high success rates (62.5% in 8 patients 88.2% in 34 patients and 100% in 12 patients) (Monzani et al. (9), Del Prete et al. (10), Tarantino (11), respectively) and low success rates (failure or only hormonal remission) have been reported (12,13). For small nodules, Mazzeo (14) and Livraghi (13) reported that PEIT is more effective in 10 mL or less nodules. Lippi et al. (8) also obtained the best results in nodules of which initial volume were less than 15 mL. Most of our patients had nodule volumes lower than 15 mL and successful results were obtained. At this point it may be expected that the higher amount of alcohol, the higher nodular shrinkage, clinical and laboratory success rates. We observed nodular shrinkage statistically correlated with the amount of ethanol injected, but cure rates did not. This finding suggests that even lower amounts of ethanol injected to prevent the leakage to surrounding tissues of nodule is sufficient to gain clinical and laboratory success in toxic nodule treatment. Finally, we also observed that PEIT was more effective in the patients who were euthyroid before the treatment. Therefore we may suggest that PEIT is more suitable for euthyroid patients with small nodules than severely hyperthyroid patients with large nodules.

Achievement of PEIT-induced euthyroidism sustained during the 2 years. In our study, PEIT was effective to lessen thyroid nodule activity rapidly and this effect lasted for a long period. On the other hand three patients were treated by surgery. One patient had clinical remission but did not have

scintigrafic remission and had increased nodule volume after PEIT. Second had severe hyperthyroidism and 23.8mL nodule volume and was taking high doses of antithyroid medication before PEIT. Low doses of antithyroid medication had to be continued in this patient during follow-up. In the third patient with high thyroid hormone levels before the treatment although 94% nodular shrinkage was seen, thyroid hormone levels did not normalize and scintigraphic nodule activity persisted. PEIT failure, observed in these patients, may be attributed to the pretreatment severity of hyperthyroidism and larger nodule volume. Thus the success of PEIT seems to be dependent partly on the nodule volume and the severity of hyperthyroidism before PEIT.

Side effects caused by ethanol injection were transient and very low. In our study no severe complications were observed related to PEIT. Probably since thyrotoxic patients were treated with antithyroid drugs before PEIT, worsening in hyperthyroid symptoms was not observed during follow-up. Pain during the injection is inevitably associated with this procedure and should not be considered as a true complication. The reason of transient dysphonia seen in one patient may be a reversible chemical effect of alcohol on recurrent laryngeal nerve as it lasted one our without any permanent effect. This complication was also observed in Monzani's study (9) but it lasted 1-4 weeks.

Incidental ethanol seepage out of the nodule capsule has been claimed to induce fibrosis of either the perinodular tissue or the thyroid surrounding structures (4). This fibrosis may lead to the technical difficulties of thyroid surgery, which may be needed thereafter. However in different studies no difficulty has been reported in evaluating the nodule capsule and surrounding vessels during the surgery (15,16). In our patients, surgery after PEIT was successfully performed without any technical problems. However, we think that ethanol seepage surrounding the nodule capsule must be carefully avoided not to lead perinodular fibrosis.

The transient increase of thyroid autoantibody titer has been reported after PEIT (10). Appearance of Graves' disease reported as a one case who refused to have surgery in literature (17). In that case nodule volume was 57.2 mL, that was very large nodule, and the amount of ethanol used was relatively high. Graves' disease which develops following PEIT may be attributed to the autoimmune response against the released of materials from thyroid tissue resultant of ethanol damage to follicular cells. In our study, we did not observe any increase in thyroid autoantibodies in concordance with Monzani's study (18). Therefore we speculate that if it is performed carefully by experienced physicians, this complication may not be occurred.

Present study confirm that PEIT can be used as an alternative therapeutic method safely in the management of the toxic thyroid nodules without any severe complication especially hypothyroidism which occurs frequently following surgery and radioiodine therapy and needs to be treated life long. This method is rapid, inexpensive, easy to perform and can be done on an outpatient basis. Moreover, there is no need of anesthesia or of bed rest for this method. If our results are confirmed by larger series, PEIT may be considered as first-line therapy in patients with toxic thyroid nodules particularly in patients without thyrotoxicosis and who have small nodules.

Prospective and randomized clinical trials comparing PEIT with surgery and radioactive iodine will provide data about the ease, efficacy and safety of alcohol injection and may lead the procedure to be accepted as a standard and first line therapy in toxic nodular goiter.

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