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## Treatment of hyperfunctioning thyroid nodules by percutaneous ethanol injection

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**Keywords:** Hot Thyroid Nodules, Treatment, Ethanol, Thyrotoxicosis, Ultrasonography

### Abstract

**Background:** Autonomous thyroid nodules can be treated by a variety of methods. We assessed the efficacy of percutaneous ethanol injection in treating autonomous thyroid nodules.

**Methods:** 35 patients diagnosed by technetium-99 scanning with hyperfunctioning nodules and suppressed sensitive TSH (sTSH) were given sterile ethanol injections under ultrasound guidance. 29 patients had clinical and biochemical hyperthyroidism. The other 6 had sub-clinical hyperthyroidism with suppressed sTSH levels ( $<0.24 \mu\text{IU/ml}$ ) and normal thyroid hormone levels. Ethanol injections were performed once every 1–4 weeks. Ethanol injections were stopped when serum  $T_3$ ,  $T_4$  and sTSH levels had returned to normal, or else injections could no longer be performed because significant side effects. Patients were followed up at 3, 6 and, in 15 patients, 24 months after the last injection.

**Results:** Average pre-treatment nodule volume [ $18.2 \pm 12.7 \text{ ml}$ ] decreased to  $5.7 \pm 4.6 \text{ ml}$  at 6 months follow-up [ $P < 0.001$ ]. All patients had normal thyroid hormone levels at 3 and 6 months follow-up [ $P < 0.001$  relative to baseline]. sTSH levels increased from  $0.09 \pm 0.02 \mu\text{IU/ml}$  to  $0.65 \pm 0.8 \mu\text{IU/ml}$  at the end of therapy [ $P < 0.05$ ]. Only 3 patients had persistent sTSH suppression at 6 months post-therapy.  $T_4$  and sTSH did not change significantly between 6 months and 2 years [ $P > 0.05$ ]. Ethanol injections were well tolerated by the patients, with only 2 cases of transient dysphonia.

**Conclusion:** Our findings indicate that ethanol injection is an alternative to surgery or radioactive iodine in the treatment of autonomous thyroid nodules.

## Background

Conventional therapy for hyperfunctioning thyroid nodules includes radioactive iodine, surgery, and long-term pharmacotherapy [1,2]. Radioactive iodine therapy is accompanied by a 10–40% risk of hypothyroidism [1–3]. A third option, introduced over the past twelve years, has been percutaneous ethanol injection (PEI) [4–19]. This method was first used in the treatment of hepatic adenomas and, subsequently, thyroid nodules [4,5,8]. It is particularly suitable for patients who are not candidates for surgery or radioiodine therapy. The tissues inside the nodule undergo fibrosis following ethanol injection [6]. The present study aims to evaluate the outcome and complications of PEI therapy for hyperfunctioning nodules. No study of this type and size has so far been carried out in Iran, a country with a significant prevalence of thyroid disorders and, until recently, an endemic goitre region.

## Methods

### Patients

This is a prospective study of the efficacy of percutaneous ethanol injection in a consecutive series of patients with a hyperfunctioning thyroid nodule. Patients meeting entry criteria were enrolled in the study and then followed up at specific times following completion of therapy. Entry criteria were a dominant hyperfunctioning thyroid nodule, as determined by technetium-99 scanning, a suppressed sensitive TSH (sTSH), and negative thyroid aspiration cytology. Patients on methimazole had their medication gradually tapered during the second and third PEI sessions, and discontinued before completion of therapy. Complete response was defined as normalisation of thyroid function tests and absence of clinical symptoms. Written informed consent was obtained from every patient. The study was approved by the relevant institutional review committee.

### Thyroid Function Tests

Thyroid function tests were measured by second-generation radioimmunoassay (Kavoshyar, Tehran, Iran), and sTSH by immunoradiometric assay (same manufacturer), with intra- and inter-assay coefficients of variation for T<sub>3</sub> of 3.3% and 7.5%, for T<sub>4</sub> of 6.8% and 8.0%, and for TSH of 5.8 and 4.9 percent. The normal ranges were T<sub>3</sub> = 80–230 ng/dl, T<sub>4</sub> = 4.5–12.8 µg/ml, and TSH = 0.2–5 µIU/ml.

### Imaging

Nodule volume was calculated automatically by the ultrasound machine, using the formula: length × width × thickness ×  $\pi/6$ , which provides an approximation to the volume of a spheroid, and is reported to be 80–85% accurate [7].

## Nodule Cytology

Every patient underwent a fine needle aspiration biopsy to rule out malignancy. In patients with multinodular goitre, the dominant nodule, as reported by <sup>99</sup>Tm scanning, was aspirated. In the single patient with two co-dominant nodules, both nodules were aspirated. The cytology report for every specimen was cystic colloid goitre, consisting of abundant colloidal material, with many haemosiderin-laden macrophages and scanty follicular cells, dispersed throughout the specimen or else forming a loose honeycomb monolayer of cells. The distinction between the latter entity and follicular neoplasia, a source of diagnostic confusion when FNA is performed in patients with a hot nodule, where the aspirate is commonly highly cellular, was, in our samples, quite clear.

## Ethanol Injection

The dimensions and volume of the nodules were measured by linear real-time ultrasonography, using a General Electric Sonochrome machine, with an 8 MHz probe. Under direct ultrasound guidance, 0.5–10 ml of sterile 95% ethanol (Pasteur Institute Production Centre – Tehran, Iran) was injected inside each nodule (0.1 ml per ml nodule volume, using a disposable plastic syringe and 22-gauge needle). Two patients had cystic nodules, which were drained completely before administration of PEI. The injection needle was kept in place for 1–2 minutes in order to avoid any ethanol leakage, and patients were advised to take oral analgesia before injection. Injections were performed once every 1–2 weeks. Patients were assessed at the end of the treatment cycle and at 3 and 6 months afterwards. Thyroid function tests were performed on 15 patients at the end of 2 years. Thyroid function tests were performed after 3–4 rounds of injection. When hormone levels were found to be within the normal range, PEI therapy was deemed successful and the injections, discontinued.

## Statistical Analysis

The repeated measures and paired-t tests were used to compare baseline and follow-up values, and Pearson's correlation test to measure the strength of the linear relationship between initial nodule size and reduction in nodule volume. Complete response was defined as a reduction in both nodule size and thyroid hormone levels, and normalization of sTSH levels.

## Results

### Demographics

35 patients (30 women, 5 men) aged 16–70 years (mean age ± SD: 38.6 ± 12.4) received PEI therapy. 18 patients (54%) had solitary hyperfunctioning nodules on <sup>99</sup>Tc scanning, with complete suppression of the remaining thyroid tissue. 16 patients (46%) had multinodular goitre with a dominant hyperfunctioning nodule. 1 patient had

**Table 1: Pre- and post-pei thyroid function in 35 patients with hot nodules**

	Initial Assessment and Follow-up				
	Before PEI (n = 35)	After PEI (n = 35)	3 months (n = 35)	6 months (n = 35)	2 years (n = 15)
T3	270.6 ± 99.6	169.05 ± 58.3*	164.5 ± 52.5*	157.6 ± 46.7*	189.2 ± 61.7‡
T4	14.9 ± 4.6	9.6 ± 3.04*	9.9±2.8*	9.4±2.4*	10.2 ± 2.46‡
TSH	0.09 ± 0.02	0.65 ± 0.8†	0.62 ± 0.8†	0.71 ± 0.8†	0.86 ± 1.5†
NV (ml)	18.2 ± 12.7	7.5 ± 5.3	-	5.7 ± 4.6	-
TTV (ml)	-	-	-	-	-

Normal Ranges: T3 = 80–230 ng/dl T4 = 4.5–12.8 µg/ml TSH = 0.2–5 µIU/ml Legend: \* Significant change [P < 0.001] compared to pre-treatment †Significant change [P < 0.05] compared to pre-treatment ‡ No significant change [P > 0.05] compared to follow-up at 6 months Abbreviations: NV: nodule volume TTV: total thyroid volume PEI: percutaneous ethanol injection

two hot nodules. 29 patients (82.9%) were hyperthyroid (suppressed sTSH and elevated T<sub>3</sub> and T<sub>4</sub> levels), and 6 patients (17.1 %) had sub-clinical hyperthyroidism with sTSH suppression and normal levels of thyroid hormones.

**Nodule Size**

Mean pre-treatment volume in the 36 nodules was 18.2 ± 12.7 ml (range = 4–44 ml). Mean post-PEI nodule volume decreased to 7.5 ± 5.3 ml (range = 1–21 ml), reaching 5.7 ± 4.6 ml (range 0.5–20 ml) at 6 months follow-up [P < 0.001]. Average volume reduction was 12.48 ± 10.6 ml, with a linear correlation between initial nodule volume and the magnitude of volume reduction: the greater the initial nodule volume, the greater the reduction in nodule volume [r = 0.94, P = 0.007].

**Thyroid Function Tests**

Sensitive TSH levels were suppressed in every patient before start of therapy, with a mean level of 0.09 ± 0.02 µIU/ml. In the sub-clinical hyperthyroid group, sTSH had risen to a mean of 0.42 ± 0.47 µIU/ml by the end of treatment, with 3 out of 6 patients still having sTSH levels below the normal range. At 3 months, the mean sTSH level in this group increased to 1.18 ± 1.3 µIU/ml, with only 1 patient showing persistent TSH suppression. At 6-months follow up, sTSH levels had normalised in all 6 patients, with a mean sTSH level of 1.15 ± 0.97 µIU/ml [P = 0.04].

In the hyperthyroid group, mean sTSH concentration at the end of therapy had risen to 0.69 ± 0.9 µIU/ml [P = 0.02]. Of the 9 hyperthyroid patients (31.0% of the hyperthyroid group) whose sTSH levels had not shown a satisfactory response to PEI therapy, only 3 patients (10.3%) had suppressed TSH at 6 months follow-up. By the end of therapy, all patients were clinically asymptomatic, with normal levels of T3 and T4 [P < 0.001]. The success rate for PEI was 91.4%, with only 3 patients (8.6%) exhibiting

**Table 2: Complications of Therapy in 35 Patients with Hot Nodules Treated by Percutaneous Ethanol Injection**

Complication	Number of patients
Pain/burning at site of injection	35
Neck pain	12
Mandibular pain	12
Dizziness/vertigo	12
Pyrexia	3
Transient dysphonia	2
Bruising at site of injection	2
Cough	1

persistent sTSH suppression with normal peripheral thyroid hormone levels. These three patients all had solitary hot nodules. Two were women, aged 37 and 25, and the third was a 44 year-old man.

**Complications**

No lasting or serious complication was observed with PEI therapy. 2 cases of transient dysphonia were reported. Both patients recovered completely. Examination by an ENT specialist showed transient vocal cord paralysis and subsequent full recovery. Table 2 shows the number of patients experiencing complications during treatment. All complications improved within minutes, except for 2 episodes of fever, which persisted for 24–48 hours, and 2 cases of transient dysphonia, which resolved fully after 1 week and 6 months.

**Discussion**

Hyperfunctioning thyroid nodules are common, yet there is controversy about their management [1,2,21]. The different modalities used include surgery, radioiodine, and

percutaneous ethanol injection [1,22]. The studies carried out over the past decade on the efficacy of PEI in the treatment of autonomous thyroid nodules indicate that it is effective, requires no anaesthesia, and carries minimal risk [19,23]. In our study, PEI also proved to be an effective treatment for patients with hyperfunctioning thyroid nodules and either clinical or sub-clinical hyperthyroidism. None of our patients reported symptoms of hyperthyroidism after PEI and all of them achieved normal peripheral thyroid hormone levels. At 3 months follow-up, only 3 patients showed persistent sTSH suppression in spite of normal thyroid hormone levels. Reduction in the volume of nodules was significant at 3 months [ $P < 0.001$ ], with an average value of  $12.48 \pm 10.6$  ml per nodule. The success rate for this study (91.3%) is consistent with that reported elsewhere (54–100%) [18,19,23,25]. Two large studies from Italy, one on 132 patients followed up over 8.5 years [23] and the other on 117 patients followed up over 5 years [24], suggest that PEI be recommended as treatment for hyperfunctioning thyroid adenoma with sub-clinical hyperthyroidism. The success rate in our patients is higher, however, than that reported in a number of larger series, notably that reported by Lippi et al [24], in which the overall success rate was 45.9% at 3 months, increasing to 73.9% at one year. 99 Tm scans were only performed before treatment in our patients; follow-up scanning may well have reduced our success rate too.

PEI can also be recommended as alternative therapy in patients at high-risk for surgery (even when the nodules are large) or for patients in whom radioactive iodine may have relative contraindication(s) [2,18,25,27]. Many authors further stress that PEI should only be carried out in centres thoroughly familiar with the technique required [28–31]. Transient dysphonia (spontaneous recovery over a period of weeks or months) has been reported in 2–5% of cases [20,30,32]. The pathology in every case has been either direct chemical injury to the recurrent laryngeal nerves, secondary to alcohol leakage outside the nodule, or nerve injury due to a sudden elevation in pressure inside the nodule. Two cases of transient vocal cord paralysis were seen in our patients; one recovered fully after 1 week, the other fully after 6 months. Real-time ultrasound used to monitor the PEI procedure can identify ethanol leakage, which shows up as a hyperechogenic area, as it is happening. One group has suggested that, in order to minimise the risk involved, a bolus of 2% Xylocaine (0.2–0.5 ml) should be injected first in order to mark the injection path before PEI itself is begun [9]. We omitted this approach because the nodules were all clearly identifiable by ultrasound and there was little risk of leakage. Studies have shown that ethanol produces coagulative necrosis of nodular tissue through hemorrhagic infarction and vascular thrombosis [33,34]. Furthermore, in the area of viable tissue surrounding the zone of biochemical ablation, en-

zyme activity is reduced. The areas of necrotic thyroid parenchyma are clearly distinguishable from the seemingly normal thyroid tissue surrounding them, which is free of any evidence of inflammation [33,34]. The probability of recurrence is virtually eliminated once granulation scar tissue replaces the nodule. Hypothyroidism is not observed even after prolonged follow-up [26,35]. Recurrence of hyperthyroidism has not been reported in patients who have had a complete response to PEI [26,35]. Our study confirms this. It should be noted that a number of our patients had multinodular goitre, with more than one hot nodule being detected on radioisotope scanning. In experienced hands, major complications of PEI, such as fibrosis of adjacent tissues or thrombogenesis within the large vessels of the neck, are unlikely [33].  $T_3$  and  $T_4$  levels in both pre-toxic and toxic patients decreased significantly [ $P < 0.001$ ], and sTSH levels increased significantly, in response to PEI [ $P < 0.01$ ]. The most important factors in predicting response to PEI are initial nodule volume and the level of skill possessed by the physician performing the procedure. Significant nodule shrinkage following PEI has already been reported in the literature [36]. Our findings confirm this. There exists a direct linear relationship between reduction in nodule volume and initial nodule volume ( $r = 0.94$ ,  $p = 0.007$ ), that is to say the greater the initial size of the nodule, the larger the reduction in size.

PEI is also effective in non-toxic thyroid nodules in young patients [6,36]. However, since the conversion rate for non-toxic nodules (to toxic nodules) is 1.2–5.7 percent/year depending on the follow-up series [37,38], many authors recommend conservative therapy for patients with non-toxic hot nodules. Furthermore, given that long-term sub-clinical hyperthyroidism is associated with increased bone turnover and accelerated bone demineralisation, and that in patients with concomitant heart disease, the increased quantity of hormone secreted by an autonomous nodule may produce arrhythmias or lead to cardiac failure, treatment of hyperfunctioning nodules with suppressed sTSH becomes necessary and PEI may be a reasonable alternative in some cases [1,2,14,36,39].

## Conclusions

We conclude that PEI is a method that is relatively inexpensive and does not require bed rest or hospitalisation. It combines convenience with avoidance of surgical risks and hypothyroidism associated with radioiodine therapy. PEI is a more practical option in younger patients because it leaves no residual surgical scar, involves no exposure to radiation, is not associated with a long-term risk of hypothyroidism, and leads to a reduction in nodule volume without recourse to surgery.

## Competing interests

None declared

## Authors' contributions

BL, MP and MHB conceived and designed the study, and drafted the original and revised drafts of the article. FA, NA, MS and MS recruited patients and performed the initial and follow-up clinical evaluations. HG and KF carried out the ultrasound examinations and ethanol injections. MRA and RBJ carried out the data analysis.

All authors read and approved the final manuscript.

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