

Techniques in Thyroidology

Treatment of Recurrent Nodular Goiters with Percutaneous Ethanol Injection: A Clinical Study of Twelve Patients

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Twelve patients who had previously undergone thyroid surgery received percutaneous ethanol injection (PEI) treatment because of recurrent nodular goiter (3 with a toxic [TN], 2 with a nontoxic cystic [NCN], and 7 with a nontoxic solid nodule [NSN]). Two of the 12 had recurrent nerve palsy contralateral to the nodule. Each patient received a mean total dose of 0.88 mL of ethanol per milliliter of nodular volume. Ethanol was injected in a mean of 3.5 sessions for solid and 3 sessions for NCN. In most cases, a slight to moderate burning pain was experienced during and for 12–48 hours after PEI treatment, and one patient experienced temporary hoarseness. One patient with TN and 2 patients with NSN became hypothyroid, 7 patients with nontoxic nodules remained euthyroid, 1 with TN became euthyroid, and a previously hyperthyroid patient with TN became subclinically hyperthyroid 1-year posttherapy. The nodule shrank by more than 50% of the pretreatment volume in all patients (8.6 ± 2.6 vs. 2.9 ± 1.2 mL in TN, and 12.3 ± 4.9 vs. 4.16 ± 2.54 mL in nontoxic nodules, pretreatment vs. 1 year posttreatment volume, respectively). With regard to the increased risk of reoperation, PEI treatment can be proposed for patients with recurrent nodular goiter requiring surgery.

Introduction

SINCE THE 1990s, ultrasound (US)-guided percutaneous ethanol injection (PEI) therapy has been proposed as an effective and safe alternative to radioiodine and surgery for the treatment of autonomous thyroid nodules (1–4). PEI treatment has been successfully applied for nontoxic solid and cystic nodules of the thyroid (5–9). In spite of reports of the long-term efficacy and safety of this therapeutic tool, there is a lack of well-defined clinical indications for this new approach (1,2,4,10). One of the most reasonable indications for PEI therapy appears to be for the treatment of nodules in patients who have previously undergone thyroid surgery. It is well known that in these cases the drawbacks of a repeated surgical procedure are augmented (11,12). In spite of this, there is no paper in the literature that focuses on the treatment of recurrent thyroid nodules with PEI.

In this study, we report on our experience with the PEI therapy of recurrent nodules in 12 patients.

Patients and Methods

Between June 1996 and January 2002, 179 patients with thyroid nodules received PEI treatment. Of the 141 patients

treated before January 2001, 12 had a nodule or nodules in a thyroid lobe that had previously been operated on. The relevant clinical data are listed in Table 1.

The pretreatment nodule volume was in nontoxic nodules 12.3 ± 4.9 mL, and that in toxic nodules was 8.6 ± 2.6 mL (9 and 3 patients, respectively). (The volumes of the nodules were calculated as described by Brunn et al. [13]). All patients with nontoxic nodules were candidates for reoperation because the compression signs were caused by the recurrent nodular goiter (5 patients suffered from dysphagia, while in 4 cases a tracheal compression in excess of 33% was detected by x-ray examination). Radioiodine therapy was undesirable in 1 patient with toxic nodule (she wished to become pregnant), while the other 2 toxic patients refused isotope treatment. Prior to PEI treatment malignancy was ruled out in all patients by fine needle aspiration cytology. The antithyroid peroxidase antibody (anti-TPO) level was normal in all patients.

Sterile 95% ethanol was injected under US control via a 23-gauge needle without anesthesia or pharmacologic sedation. Depending on the nodule size, the ethanol dose injected in each session varied in the range 1–6 mL; it was administered slowly (over 2 minutes). (For cystic nodules, 90% of the

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cystic fluid was aspirated prior to the ethanol injection.) Each patient received a mean total dose of 0.88 mL ethanol (range, 0.34–1.57 mL) per milliliter of nodular volume. The ethanol was injected in a mean of 3.5 (range, 2–5) outpatient sessions for solid and in 3 sessions for pure cystic nodules. Two patients (both with nontoxic solid nodules) had recurrent nerve palsy contralateral to the recurrent nodule. They were treated extremely carefully in order to minimize the risk of even temporary bilateral recurrent nerve palsy. The ethanol was given more slowly in these cases (over 5 minutes) and the amount of ethanol administered in each session was only half the usual. Moreover, they were inpatients during and for 24 hours after each sessions.

During the PEI treatment, 2 patients were treated with methimazole, which was stopped on the day of the last PEI session.

Follow-up protocol included physical examination, US, and thyrotropin (TSH), and free thyroxine (FT₄) determinations repeated after 1.5, 4.5, and then every 12 months after treatment. One year after the therapy, anti-TPO and tracheal x-ray examination were performed in all patients and a scintiscan was performed in the toxic patients.

For the nontoxic nodules, the outcome of the PEI treatment was determined according to the US result. Success was defined as shrinkage of the nodule to half or less of the pretreatment volume on 4.5 months and every later follow-up occasion. For the toxic nodules, complete success required two additional conditions to be fulfilled: normalization of the TSH and FT₄ levels and restoration of the extranodular uptake on the scintiscan. Success for the toxic nodules was partial if either the TSH level or the extranodular uptake remained abnormal.

Results

No important adverse effects were observed (Table 2). We administered 42 PEI sessions. In 5 of the 42 cases, the patients had no complaints. In the remaining cases, only a slight to moderate burning and tensing pain were experienced during and for 12–48 hours after PEI treatment. In 26 cases no analgesic was used, while in 11 cases the complaint was resolved after using analgesic tablets at one or two occasions (9 and 2 cases, respectively). One patient reported a change in her voice 1 hour after last PEI session, this change lasting for approximately 30 minutes. The laryngeal status did not show any abnormalities on the following day. No other cases of recurrent nerve palsy or voice change was observed. The anti-TPO levels remained normal in all cases.

Nontoxic nodules

The therapy was successful in all patients (Fig. 1). A continuous shrinkage of the nodule was observed during the first posttherapy year (12.3 ± 4.9 vs. 4.16 ± 2.54 mL, pretreatment vs. 1 year posttreatment volume, respectively). The TSH and FT₄ levels were unchanged in 2 cystic patients (1.95 mIU/L and 16.7 pM/L vs. 2.1 mIU/L and 15.5 pM/L, before and 1 year posttherapy, respectively). The TSH level was increased and the FT₄ level was decreased after PEI in the 5 patients with nontoxic solid nodules who remained euthyroid without levothyroxine therapy (3 patients) or with levothyroxine therapy at the same dose (2 patients), but the difference was not significant (1.59 ± 1.28 mIU/L, and 14.0 ± 3.64 pM/L vs. 2.03 ± 0.61 mIU/L and 12.9 ± 2.17 pM/L, before and 1 year posttherapy, respectively). Two patients with solid nodules had become hypothyroid by the 1.5- and 4.5-

TABLE 1. PRETREATMENT CLINICAL DATA ON PATIENTS WITH RECURRENT THYROID NODULES

Type of nodule	Gender, age	Year of thyroid operation	Size of nodule (mL)	Recurrent nerve status	Hormonal status	
					TSH (mIU/L)	FT ₄ (pM/L)
Nontoxic, cystic ^a	F, 56	1980	8.3	Intact	1.23	17.8
Nontoxic, cystic ^a	F, 49	1973	7.8	Intact	2.67	15.5
Nontoxic, solid	F, 78	1951	20.5	Intact	2.90	9.93
Nontoxic, solid	F, 46	1974	5.8	Damaged contralateral	1.03 ^b	12.4
Nontoxic, solid	F, 51	1978	7.97	Intact	3.67 ^b	12.0
Nontoxic, solid	F, 61	1993	9.48	Damaged contralateral	0.72	11.0
Nontoxic, solid	F, 65	1990	15.8	Intact	0.59	20.1
Nontoxic, solid	F, 55	1985	18.0	Intact	2.06	13.1
Nontoxic, solid	F, 53	1971	16.7	Intact	1.95	14.5
Toxic ^c	F, 36	1989	4.7	Damaged ipsilateral	0.001	17.2
Toxic ^c	F, 72	1979	11.1	Intact	0.001	23.1
Toxic	F, 32	1990	10.0	Intact	0.001	37.6

Normal range of TSH is 0.3–3.5 mIU/L, while that of FT₄ is 9.1–23.8 pM/L.

^aPreviously evacuated, but refilled cysts.

^bThe patients were on levothyroxine therapy (75 µg/d and 125 µg/d, respectively).

^cMethimazol-treated patients, currently in a subclinically hyperthyroid hormonal status. TSH, thyrotropin; FT₄, free thyroxine.

TABLE 2. SIDE EFFECTS OBSERVED DURING AND AFTER PEI TREATMENT

	<i>Cystic nodules</i>	<i>Solid nodules</i>
Mild to moderate pain during PEI session	2/6 sessions	37/42 sessions
Mild to moderate pain lasting for 12–48 hours after PEI session	2/6 sessions	33/42 sessions
Hypothyroidism	—	3 patients
Fever	—	2 patients
Granulomatous reaction	—	1 patient
Hematoma	—	1 patient
Transient hoarseness	—	1 patient

PEI, percutaneous ethanol injection.

month controls. Both these patients had undergone bilateral subtotal thyroidectomy prior to the PEI treatment. These patients are euthyroid with 50 and 125 μg levothyroxine, 1 year and 2 years posttherapy, respectively.

The tracheal compression was completely relieved in two cases while in two other cases the degree of compression decreased from 33% to minimal. The dysphagia was completely relieved in four patients, whereas it merely decreased in the fifth.

Toxic nodules

Complete success was achieved in two cases, and partial success in the third. The nodule shrank by more than 50% of the pretreatment volume in all patients (8.6 ± 2.6 vs. $2.9 \pm$

1.2 mL, pretreatment vs. 1 year posttreatment volume, respectively). One patient had become hypothyroid by the 4.5-month control, and required 75 μg levothyroxine for normalized thyroid status. Another patient remained euthyroid and had a normal scintiscan 1 year posttherapy. The third patient had normal FT₄ and triiodothyronine (T₃) values on all follow-up occasions, but the TSH level was continuously below the normal value. This was the only patient whose extranodular thyroid tissue remained suppressed on the scintiscan 1-year posttherapy.

The best results were obtained in the two patients with cystic nodules (the nodules decreased to 16% and 20% of the pretreatment volume). Regarding solid nodules, those smaller than 10 mL demonstrated a greater relative decrease in size than those larger than 10 mL (patients with nodules

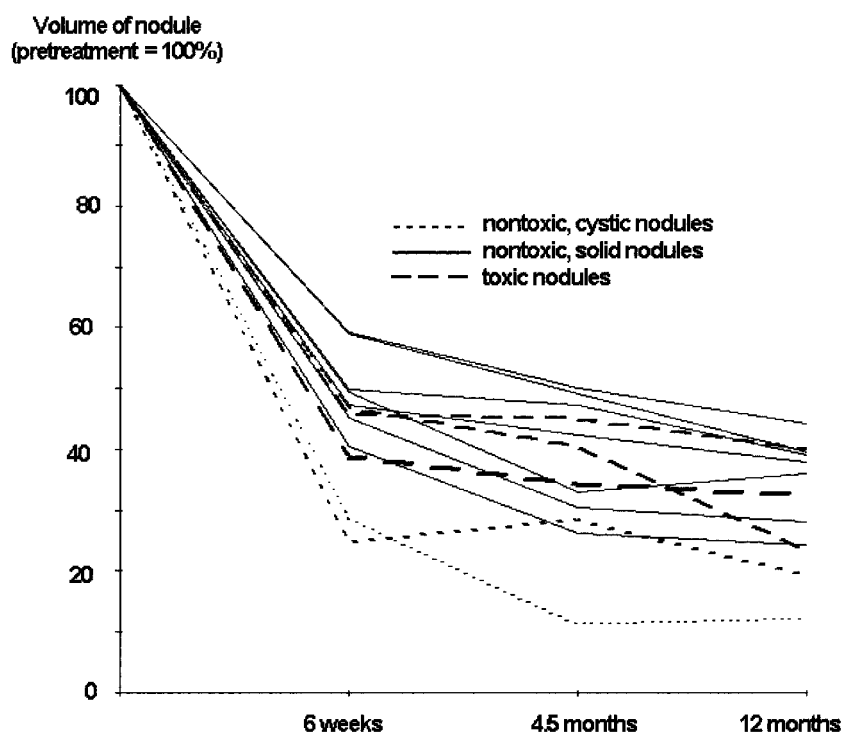


FIG. 1. Effects of percutaneous ethanol therapy of recurrent nodular goiters on the size of the nodule.

larger than 10 mL, 37.6% and patients with nodules smaller than 10 mL, 33.6%) of the nodule 1 year posttreatment (pretreatment volume 100%).

Discussion

PEI treatment seems to offer effective therapy for various types of nodular thyroid diseases. While the rate of success does not reach that of surgery, there are two situations in which PEI is more advantageous than thyroid surgery. The first is well known and mentioned in most publications: PEI can be performed when surgery is considered high risk because of the state of health of the patient (1,3,4,6,14,15). The second, less emphasized condition is that PEI treatment has no irreversible sequelae, such as laryngeal nerve palsy, hypoparathyroidism, or in most cases hypothyroidism.

The latter condition is particularly important in those patients who have previously undergone thyroid surgery and have a recurrent nodular goiter. In these cases the risk of recurrent laryngeal palsy is enhanced. Whereas the rate of permanent recurrent nerve palsy is approximately 2% in the first thyroid operation with an experienced surgeon, this risk is increased 2- to 8-fold in the event of reoperation (12,16,17). The risk of iatrogenic parathyroid gland resection is also typically increased on repeated surgery (18). Moreover, there are patients who have undergone previous surgery with extreme damage: patients who suffer from recurrent laryngeal palsy and have a recurrent nodule requiring surgical therapy on the contralateral side.

There is no systematic study in the literature that focuses on PEI treatment in thyroid patients who have undergone previous surgery. There have been reports where a few patients with recurrent nodules are mentioned among others (2). Our results demonstrate that PEI therapy is an effective treatment without major risks in patients who have already undergone surgery. We attained complete success in all but 1 of 12 patients. The treated nodule shrank to less than half of the pretreatment volume in all patients. In 1 previously hyperthyroid patient, we reached only partial success: this patient was able to stop methimazole therapy, and the compressive signs caused by the toxic nodule were also relieved but the extranodular thyroid remained suppressed.

Although permanent recurrent nerve palsy is not among the side effects of PEI, temporary palsy does not occur infrequently after PEI (1,2,19). This has no major drawbacks in most cases. However, in patients whose recurrent nerve contralateral to the recurrent nodule is damaged before therapy, even temporary bilateral palsy would have dramatic consequences. These patients should be treated extremely carefully. We had two patients with this condition. In these cases, the ethanol was administered more slowly (over 5 minutes instead of 2) and the amount of ethanol given in a session was only half of the usual dose. Nevertheless, the total ethanol dose was in the usual range (0.68 and 0.77 mL per 1 mL nodular tissue).

A special technical problem arises in patients whose thyroid has previously been operated on. Most of these thyroids continue to appear abnormal on US. This is not surprising because US is a sensitive tool with which to detect structural abnormalities irrespective of their origin (a technical artifact as a consequence of the previous operation or a true nodule that has developed or been left in the treated lobe). There are

major practical consequences primarily in smaller echo abnormalities where it may be difficult to decide whether a discrete echo abnormality is a true recurrent nodule or not. In patients with larger nodules that require reoperation or PEI, this problem is not as difficult, because the larger the lesion, the higher the probability of its nodular origin. Despite this, we should proceed with care: the symmetrical shape, the regular border, the homogenous echopattern, and the presence of the halo sign are characteristic of a nodule, while a non-symmetrical echoabnormality with an irregular border and a mixed echo pattern could reflect a technical artifact or a granulomatous reaction around a surgical thread.

It should be mentioned that PEI cannot be performed in all patients with recurrent nodules. Radioiodine therapy is the treatment of choice for recurrent toxic nodules. Patients with solitary nontoxic nodules are the ideal candidates for PEI treatment. On the other hand, in our practice, recurrent nodules are multiple in more than two thirds of the cases. This is a consequence of the major cause of recurrence: an iodine deficiency. Iodine-deficient goiters are typically multinodular (20). Nevertheless, those multinodular patients who have one dominant nodule or two well-circumscribed nodules leading to an indication of reoperation may also reasonably undergo PEI therapy. (This was the case in 2 of the 12 patients with solid nodules.) In our practice, approximately 60% of patients with recurrent nodular goiters may undergo PEI instead of surgical treatment.

In comparison with surgery or radioiodine treatment, PEI has an important advantage: hypothyroidism develops only rarely after the therapy (1,19). We experienced only 2 cases of hypothyroidism after PEI treatment in 165 patients in whom there had been no previous surgery or iodine therapy. In contrast, it seems logical that PEI treatment in patients who have previously been operated on may lead to hypothyroidism. This was observed in 3 of our 12 patients. All of them underwent bilateral subtotal thyroidectomy; moreover, in 1, radioiodine therapy was also performed prior to PEI. The combined effect of the previous ablation and PEI treatment led to hypothyroidism.

We consider that the statement of Bennedbaek and coworkers from 1997 remains almost completely valid today: PEI must be regarded as an experimental procedure and should be reserved for patients who cannot or will not undergo surgery or radioiodine therapy (1). On the other hand, there are subsets of patients for whom PEI treatment can be proposed. Patients with recurrent nodular goiter requiring surgery may comprise one of these subsets. Prospective and properly controlled investigations will be needed to assess the role of PEI in our therapeutic spectrum.

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