Percutaneous ethanol injection for benign cystic thyroid nodules

Mustafa T. Ahmed[a], Mohamed B.M. Kotb[a], Mohamed S. Shahine[b], Hassan M. Harby[c], Mahmoud T.A. Mohamed[d]

Departments of [a]General Surgery, [b]Maxillofacial Surgery, Faculty of Medicine, Assiut University, [c]Department of General Surgery, Assiut University Hospital, [d]Lecture of General Surgery, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Hassan M. Harby, Demonstrator, Department of General Surgery, Assuit University Hospital, Assiut, Egypt
Postal Code: 71511;
e-mail: harby1990hassan@gmail.com

Received 29 October 2018
Accepted 29 November 2018

Journal of Current Medical Research and Practice
May-August 2018, 3:110–114

Aim
The aim of this study was to evaluate the efficacy and safety of percutaneous ethanol injection (PEI) in managing predominantly cystic benign thyroid nodules in euthyroid individuals and avoid complication of surgery, provide symptomatic, cosmetic improvement, decrease the hospital stay and rapid recovery.

Patients and methods
The study is an experimental clinical trial. Twenty patients (34.20 ± 7.52 years; 60% women) with symptomatic benign thyroid cysts were included. In all cases, cytology before treatment, thyroid function before and after PEI, maximum cyst diameter, and volume were determined. PEI was conducted using 99% sterile ethanol, and pain perceived by the patients was assessed. After follow-up, final cyst diameter and volume were determined.

Results
The patients mean age was 34.20 ± 7.52 years, and 60% were females. A single session of PEI was required to complete the procedure. Mean initial maximum cyst diameter was 4.3 cm. Mean reduction in the cyst volume was 94.38%±4.04. During PEI, 40% of patients experienced pain. No complications of PEI were observed. After 6 months of follow-up, cysts were reduced more than 95% in 75% of patients, and reduced less than 95% in 25% of patients.

Conclusion
PEI can be the first-line treatment of benign thyroid cysts. It is a highly efficacious and safe technique with improvement in clinical conditions, with very low recurrence rate, and with no complications except pain associated with injection, which can be managed by analgesic.

Keywords:
benign thyroid cysts, percutaneous ethanol injection, volume of reduction

J Curr Med Res Pract 3:110–114

2357-0121

Introduction

Thyroid nodules are common discreet lesions in the parenchyma of thyroid gland which can be either palpated or detected during imaging like ultrasonography (US) [1].

Clinically palpable thyroid nodules have a prevalence of 4–7% in the general population [2]. However, the prevalence increases to 20–76% when US is used for detection [3].

Goiter and the associated thyroid nodules result in anxiety, cosmetic disfigurement, and rarely compressive symptoms necessitating surgical removal, a procedure inherently associated with risks and complications [3,4].

Percutaneous sclerotherapy has been suggested to be an effective alternative, especially in patients with cystic thyroid lesions [4].

Simple cystic (purely cystic) and complex cystic (having both cystic and solid components) nodules constitute 6–28% of all thyroid nodules, are usually benign, filled with cellular debris or blood, and are a result of degeneration or hemorrhage into a hyperplastic nodule or adenoma [4].

Among the various compounds (sodium tetradocyl sulfate, hydroxypolyethoxydodecan, tetracycline, and ethanol) tried for sclerosis of cystic thyroid nodules, outcomes are best and most studied with ethanol [5].

Since the late 1990s, sonography-guided percutaneous ethanol injection (PEI) has emerged as a safe and effective conservative alternative to surgical excision [6].

The injection of 95–99% ethanol into the cyst cavity induces thrombosis of small vessels and coagulative necrosis surrounded by interstitial edema and granulomatous inflammation, followed by fibrosis, shrinkage, and reduction in the volume of the lesion [6,7].

However, data on outcomes of PEI in resolution of thyroid nodules are highly variable in different studies (success rate: 38–85%), which may be owing to different populations studied and the heterogeneous nature of thyroid nodules evaluated, ranging from purely cystic to purely solid nodules [8-12].

Patients and methods

This study was performed at General Surgery Department, Assiut University Hospitals, from January 2017 to August 2018. A total of 20 patients (34.20 ± 7.52 years; 60% women) with symptomatic benign thyroid cysts were included (IRB:17100281).

Inclusion criteria were as follows:
(1) Adult male or female patient with cystic thyroid nodule
(2) Presence of pressure symptoms or cosmetic problems
(3) Patients presented with benign lesion confirmed by histopathological examination through fine-needle aspiration cytology
(4) Serum levels of thyroid hormone thyrotropin within normal limits.

Exclusion criteria were as follows:
(1) Nodules showing malignant features (i.e. speculated margins, markedly hypoechoic, microcalcification or macrocalcification) at US finding
(2) Solid thyroid nodules
(3) Mixed thyroid nodules (cystic with solid component).

Before the study, all patients were subjected to thyroid function tests [thyroid-stimulating hormone, free triiodothyronine (T3), and thyroxine (T4)] before PEI.

The study was performed with each patient in the supine position with mild neck extension. The neck skin is carefully disinfected. Adequate sterility is also ensured by the use of sterile devices (e.g. probe cover, US gel, and gloves). No medication was administered before the procedure. The procedures were performed with US guidance by GE Logic P6 (General Electric Company, New York) Ultrasound device. Before the treatment, the diameter of each nodule was measured, and the volume of each nodule was calculated. Doppler US was used to locate vessels along the approach route to prevent serious bleeding.

The puncture site was anesthetized with 2% lidocaine, and the skin was not incised so as to prevent unnecessary scar formation.

The needle was then inserted and cautiously directed into the lesion step by step, while kept in full sight by US imaging, with minor adjustments of the probe after the needle tip was placed into the central portion of the cyst; the internal fluid contents were aspirated to the maximal extent.

After complete fluid aspiration, 99% sterile ethanol is carefully injected into the cyst under visualization of US as a hyperechoic material which progressively refills the cyst as shown in Fig. 1.

Some critical issues that were considered during the procedure were as follows:
(1) The needle tip was kept under continuous surveillance, especially during the phase of ethanol infusion
(2) Abrupt movements were avoided to prevent damaging the cyst walls
(3) If the cyst contents were viscous, this viscous fluid was aspirated by using a large-bore needle followed by irrigation with normal saline to remove viscous material attached to the cystic wall.

After this, the needle was withdrawn, and the infused ethanol was left inside the cyst to prolong its sclerotic effect. This was followed by measurement of the diameter of each cyst after ethanol injection.

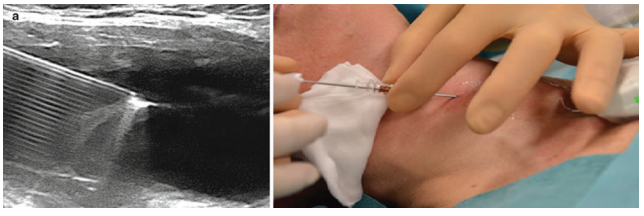
Assessment of complications was performed during and immediately after the procedure to assess its safety.

Procedure-related pain was graded into four categories:
(1) No pain or mild pain similar to pain experienced during the lidocaine injection
(2) Pain is greater than that of the lidocaine injection but not requiring medication
(3) Pain that required medication
(4) The procedure was incompletely terminated because of severe pain.

Following the procedure, each patient was observed for 30 min while still in the hospital.

Patients were followed up weekly for 1 month, after 3 months, and 6 months thereafter. US examination was performed at each appointment to evaluate the characteristics and volume of the residual lesion, and assess complication such as recurrence and abscess

Figure 1



Ultrasonography during the process of ethanol injection.

formation, and also the patients underwent thyroid function test after PEI.

In each patient, the percentage of volume reduction was calculated by the formula [(Vol 1 – Vol 2)/Vol 1]×100, in which Vol 1 is the initial cyst volume and Vol 2 the final cyst volume.

Results

This study included 20 patients with symptomatic thyroid cyst, including 12 (60%) female patients and eight (40%) male patients. Overall, six patients were aged less than 30 years, nine patients were aged 30 to less than 40 years, and five patients were older than 40 years, with mean age of 34.20 ± 7.52 years, as shown in Table 1.

Prepercutaneous and post-PEI thyroid functions:

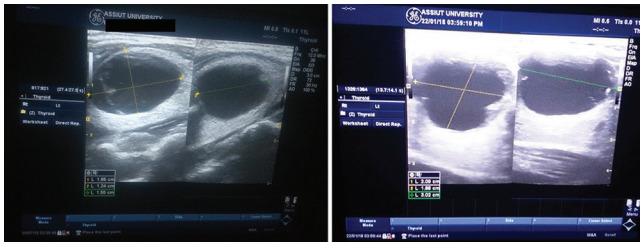
Follow-up of the thyroid function found the following:
(1) The mean T3 level before PEI was 1.14 ± 0.21 ml/dl and the level of T3 after PEI was 1.16 ± 0.20 ml/dl (normal level of T3: 0.79–1.58 ml/dl)
(2) The level of T4 before PEI was 7.78 ± 1.46 ml/dl, and it level after PEI was 7.80 ± 1.27 ml/dl (normal level of T4: 4.9–11.00 ml/dl)
(3) TSH level before PEI was 1.14 ± 0.5 μIU/ml, and its level after PEI was 1.20 ± 0.53 μlU/ml (normal level of TSH: 0.35–5.5 μIU/l) as shown in Tables 2–4.

Findings of neck US of the studied patients were as follows:
(1) It was found that the volume of the thyroid cysts at the time of examination was 4.3, with mean of 5.04 ± 3.51, as shown in Fig. 2
(2) After 3 months of follow-up, the thyroid cysts was 0.9, with mean of 1.25 ± 1.16, as shown in Fig. 3
(3) After 6 months of follow-up, the cyst size reached to 0.2 cm, as shown in Table 5 and Fig. 4.

Postoperative complications in this study were as follows:

In this study, we found that the most frequent complications postoperatively was pain (which scores mentioned above), which occurred in eight patients (40%), and other complications included recurrence of the lesion in 0%, bleeding from the procedure in 0%, and abscess formation in 0%, as shown in Table 6.

Figure 2



Cyst before ethanol injection.

Percentage of reduction in the size of the cyst

In this study, we calculate the percentage of reduction in the size of the cyst by the formula [(Vol 1 – Vol 2)/Vol 1]×100, in which Vol 1 is the initial cyst volume and Vol 2 the final cyst volume after 6 months of follow-up. We found the following results:
(1) In 75% of the patients, the thyroid cyst reduces in volume to more than 95%
(2) In the remaining 25% of the patients, the reduction in the size of the cyst was less than 90%, with mean volume reduction of 94.38 ± 4.04%, as shown in Table 7.

Discussion

This study was performed at General Surgery Department, Assiut University Hospitals, from January 2017 to August 2018.

This study included 20 patients with symptomatic thyroid cysts, with mean age of ~34.20 ± 7.52 years. Overall, 60% of the patients were females and 40% males. Antonelli

Table 1 Age distribution of the studied patients

Age (years)	*n*=20 [*n* (%)]
<30	6 (30.0)
30 to <40	9 (45.0)
≥40	5 (25.0)
Mean±SD	34.20±7.52
Range	25.0-55.0

Table 2 Triiodothyronine

Triiodothyronine (ml/dl)	Preoperative (*n*=20)	Postoperative (*n*=20)	*P* (Wilcoxon signed-rank test)
Mean±SD	1.14±0.21	1.16±0.20	0.479*
Median (range)	1.2 (0.8-1.4)	1.2 (0.8-1.4)	

*$P<0.05$, statistical significant difference.

Table 3 Thyroxine

Thyroxine (ml/dl)	Preoperative (*n*=20)	Postoperative (*n*=20)	*P* (Wilcoxon signed-rank test)
Mean±SD	7.78±1.46	7.80±1.27	0.340*
Median (range)	7.9 (4.9-10.0)	7.9 (4.9-9.5)	

*$P<0.05$, statistical significant difference.

Table 4 Thyroid-stimulating hormone

Thyroid-stimulating hormone (μlU/ml)	Preoperative (*n*=20)	Postoperative (*n*=20)	*P* (Wilcoxon signed-rank test)
Mean±SD	1.14±0.53	1.20±0.53	0.017*
Median (range)	1.0 (0.6-2.6)	1.0 (0.7-2.7)	

*$P<0.05$, statistical significant difference.

Table 5 Size of the cyst

Size of the cyst	At examination	After 3 months	After 6 months	*P* (Wilcoxon signed-rank test)[a]	*P* (Wilcoxon signed-rank test)[b]
Mean±SD	5.04±3.51	1.25±1.16	0.34±0.51	0.001*	0.001*
Median (range)	4.3 (0.3-13.8)	0.9 (0.1-5.0)	0.2 (0.0-2.1)		

[a]Comparison between 'at examination' and 'after 3 months'.[b]Comparison between 'at examination' and 'after 6 months'.*P<0.05, statistical significant difference.

Table 6 Complications

Complications	*n*=20 [*n* (%)]
Pain	8 (40.0)
Recurrence	0 (0.0)
Bleeding	0 (0.0)
Abscess formation	0 (0.0)

Table 7 Percentage of volume reduction

Percentage of volume reduction	*n*=20 [*n* (%)]
<90%	5 (25.0)
90-95%	4 (20.0)
>95%	11 (55.0)
Mean±SD (range)	94.38±4.04 (84.95-99.52)

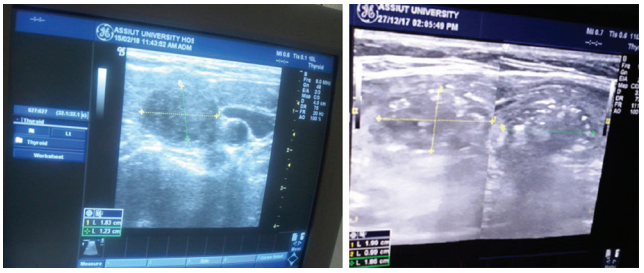
et al. [13] found that mean age was ~44 ± 8 years (70% females and 30% males) [13], whereas in the study by In *et al.* [14], the mean age was 45 years, with range of 16–78 years (74% females and 26% males) [14]. Reverter *et al.* [15] found that the mean age was ~46 ± 10 years, with 82% females and 16% males [15]. This statistic deference may be owing to different sample size.

In this study, all patients were symptomatic and the main complaint was palpable neck mass and cosmetic problem, mainly in female patients. This is in accordance with Reverter *et al.* [15] and Sung *et al.* [16] who reported that compressive symptoms or esthetic complaints were the main complaint of the included patients.

In this study, US was done for all cases before injection of ethanol, and injection was done in only pure cystic thyroid lesion. Antonelli *et al.* [13] found that the US showed the presence of an anechoic cystic lesion with no solid component, a smooth, thin wall, and a diameter greater than 1 cm, whereas in In *et al.* [14], nodules with more than 10% solid components were classified as thyroid cysts and included them in the study, whereas those with 50–90% cystic components were classified as predominantly cystic thyroid nodules [14]. Sung *et al.* [16] US was a cystic thyroid nodule (cystic portion more than 90% and solid component in some cases).

In this study, it was found that the cyst diameter by US before process of PEI was 4.3 with mean ± SD 5.04 ± 3.51, whereas Reverter *et al.* [15] found that the cyst diameter was 3.5 ± 1.0 cm before the process of PEI and In *et al.* [14] found that before process of PEI the cyst diameter was 2.9 cm. This deference in the cyst diameter in these different studies may be owing to endemicity of this disease in different localities.

Figure 3



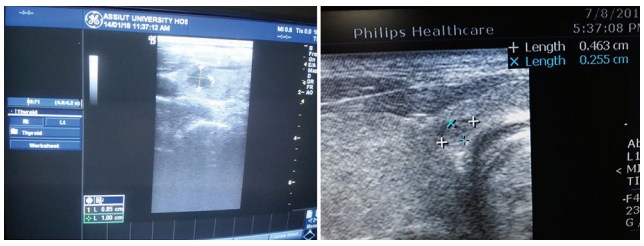
Cyst after 3 months of ethanol injection.

After PEI was done, the patients were followed up weekly for 1 month, after 3 months, and 6 months thereafter. US examination was performed at each appointment to evaluate the characteristics and volume of the residual lesion and assess the recurrence and other complication such as abscess formation.

This study found that the requirement was a single session of ethanol injection (PEI) for permanent reduction in cysts, whereas In *et al.* [14] in their study found that repeat ethanol injection was performed at 1–3 months after the initial ethanol injection, and this is called 'two-stage ethanol injection'. In two-stage ethanol injection, the initial ethanol injection was a simple injection of a small amount of ethanol for the liquefaction of viscous contents. Reverter *et al.* [15] stated that the required number of PEI for permanent reduction in cysts and a symptom-free situation was such that 45.5% of cases required one session of PEI, 31.8% of cases required two sessions of PEI, and 13.6% of cases required three sessions of PEI. Moreover, two patients with the largest cysts were treated four and six times, correspondingly. This difference may be owing to that the initial calculated cyst volume was significantly greater in the group of patients who required three or more PEI procedures compared with those treated with one or two PEI, respectively.

In this study, after follow-up of 3 months, it was found that the cyst volume by US was 0.9 (0.1–5.0) ml., with mean ± SD 1.25 ± 1.16. Further follow-up at 6 months shows that the volume of cyst was 0.2 ml with mean ± SD 0.34 ± 0.51 with reduction in the cysts volume of more than 95% in 75% of the included patients, and in 25% of the patients, the cysts were reduced less than 90%, with mean reduction in the cysts volume ranging from 84.95 to 99.52%. Sung *et al.* [16] found that the mean volume reduction of the ethanol

Figure 4



Cyst after 6 months of ethanol injection.

ablation group was 96.9% after 6 months of follow-up.

However, Reverter *et al.* [15] after 1–2 years of follow-up stated that the mean calculated cyst volume reduction was 85.9 ± 14.7%. Cysts were reduced more than 70% in volume in 86.3% of patients, more than 80% in 61.9%, and more than 90% in 42%. The final mean maximum thyroid cysts diameter was 1.3 ± 0.6 cm. Total disappearances of the cysts were observed in three cases. This may be owing to repeated session of PEI and long-term follow-up. In *et al.* [14] found that the reduction of cyst ranged ~93.3% after 12–24 months after PEI. This difference depends on a variety of factors, including the initial cystic component volume, volume of injected ethanol, percentage of the solid component of the cyst, and nature of the aspiration.

In this study, all patients showed complete resolution of the initial symptoms, including a palpable anterior neck mass, neck discomfort, and cosmetic problems [14]. All the patients showed complete resolution of the initial symptoms, such as neck mass, neck discomfort, and other cosmetic problems.

In this study, we found that the most frequent complications after procedure was pain which occurred in eight patients (40%) and other complications included recurrence of the lesion in about 0% and, bleeding from the procedure in about 0%, and abscess formation in about 0%.

Reverter *et al.* [15] found the sensation of pain reported during PEI was virtually absent in 39.1% of patients, mild in 43.5% of patients, and moderate in 17.4% of patients. The patients were requested to grade the sensation of pain experienced with the alcohol injection immediately after the procedure, using a visual scale of 10 cm between the absence of pain (0) and excruciating pain (10), in which each 1/3 of the scale corresponded from the lowest to the highest, to the following categories: mild pain, moderate pain, and severe pain.

In all cases, there was a transient sensation of pain, which was relieved within minutes. No patient felt intense pain and none experienced other complications. In *et al.* [14] found that 24.2% of patients experienced mild pain either during or several minutes after the procedure according to Visual Analog Scale for Pain, and there were no serious complications during or after PEI. In the follow-up US after PEI, there were no cases of recurrence.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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