

## Effect of percutaneous ethanol injection in treatment of non-functioning benign solid thyroid nodules

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### ABSTRACT

**Objective:** Percutaneous Ethanol Injection (PEI) is a simple effective procedure especially in the treatment of autonomous and cystic thyroid nodules. In this study, we investigated the effect of PEI in volume reduction of nonfunctioning benign solid thyroid nodules.

**Methodology:** In a prospective study, 62 euthyroid patients with benign thyroid nodules were selected consecutively by endocrinologist from those being visited at endocrinology clinics of Tabriz University of Medical Sciences, Iran during January 2007 to January 2008. The injection volume was set as two third of the nodule total size in cm<sup>3</sup> according to the ultrasonographic measurements with an upper limit volume of 10cc. The patients were followed up one week after injection for possible complications, and then 3 and 6 months later for evaluation of efficacy of intervention by ultrasound. Student t and Chi-square tests were used for statistical analysis and a P-value <0.05 was considered as statistically significant.

**Results:** The data of 57 patients was used in the final analysis among which 5(8.8%) were male and 52(91.2%) were female. After six months of follow-up, the reduction in nodule size was <30% in 15(26.3%) patients, between 31% and 50% in 14(24.6%) patients, and more than 50% in 28(49.1%) patients which was statistically significant (P = 0.001). Local pain in first week after injection was the main complication.

**Conclusion:** Percutaneous Ethanol Injection (PEI) therapy can be a safe and effective method in the treatment of benign solid nonfunctioning thyroid nodules.

**KEY WORDS:** Thyroid nodules, Management, Percutaneous Ethanol Injection.

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### INTRODUCTION

The prevalence of thyroid nodules is on the rise; while less than 5% of thyroid nodules are detectable by cervical palpation, autopsies indicate that thyroid nodules with normal function are present in up to 50% of the normal population.<sup>1</sup> As ultrasonographic studies result in diagnosis of a larger amount of non-palpable thyroid nodules,<sup>2</sup> endocrinologists are benefitting more of this instrument in their screening tests resulting in a higher diagnosis rate of thyroid nodules.<sup>3</sup> When a thyroid nodule is detected, in addition to the patient preoccupation, a major concern for the physician is to choose the appropriate treatment. Other than surgical intervention, which is necessary in just a few cases, a large variety of treatment options are in prospect

which include: monitoring without intervention; levothyroxine suppression therapy; ablation by laser, radiofrequency or  $^{131}\text{I}$  and percutaneous ethanol injection.

Percutaneous ethanol injection (PEI) is a simple effective procedure especially in the treatment of autonomous and cystic thyroid nodules, which has recently attracted more attention.<sup>1,4-7</sup> The ethanol induced tissue damage results in coagulation necrosis, vascular thrombosis and hemorrhagic infarction which is finally replaced by granulation tissue ending in a progressive regression of the nodule and the resultant tissue scar.<sup>8</sup> Besides needing several injections, this method is accompanied by some complications; however, a successful PEI prevents aggressive interventions and provides fertile ground for less invasive procedures such as endoscopic surgery.<sup>9</sup> PEI has been studied in the treatment of various thyroid nodules including normal function nodules; however, its safety and effectiveness remains controversial.<sup>1,4-8</sup> Even though, PEI has been recommended in some studies as a safe effective therapeutic alternative in the treatment of non-functional thyroid nodules.<sup>1,10</sup>

The primary goal in the treatment of autonomous thyroid nodules is clinical improvement of the thyrotoxicosis; however, the nodule size is of greater importance in the non-functioning nodules. In this study, we investigated the effect of injecting 96% ethanol in non-functioning benign solid thyroid nodules on the nodule size, as a marker of healing.

## METHODOLOGY

After the study protocol being approved by the Research Ethics Committee of Tabriz University of Medical Sciences, 62 euthyroid patients with benign thyroid nodules were evaluated in a prospective study. Subjects with clinically solitary thyroid nodule that they had normal thyroid function tests, greater than 75% solitary component by ultrasonography, the largest diameter  $>1$  and  $<6$  cm, and benign cytology were included. Subjects with  $<15$  and  $>75$  year old, history of hypersensitivity to ethanol, bleeding tendency, advanced renal or hepatic failure, unwillingness to seek treatment and give written consent were excluded. The patients were selected from the patients visiting at endocrinology clinics of Imam Reza Hospital, Tabriz University, and the authors' private clinics during January 2007 to January 2008. The study protocol follows the Helsinki declaration for human research and informed written consent was obtained.

After the patients being fully informed of the study process and objectives, demographic information including age, sex, time since nodule formation and drug history was obtained. A fine needle biopsy (FNA) was performed to confirm the benign nature of the nodules; all the patients were previously evaluated for normal function of the nodules using thyroid function tests. Size of the nodules was measured in a ultrasonographic evaluation at Imam Reza Hospital Radiology Department. At the same session of sonography, 96% ethylic alcohol was injected into the nodule by means of a 10 cc syringe with a 23 Gauge needle. The injection volume was set as two third of the nodule total size in  $\text{cm}^3$  according to the ultrasonographic measurements with an upper limit volume of 10 cc. The patients were visited within one week for possible complications, and then 3 and 6 months later; an ultrasonographic evaluation of the nodule size was made by a sonographer and physical examination was performed by an endocrinologist during the two last follow-up visits. The reduction in nodule size was defined as  $<30\%$  (no response), between 31% and 50% (moderate response), and more than 50% (desirable response).

SPSS software version 16 (SPSS Inc., Chicago, IL) was used for statistical analysis. Student t-test and Chi-square test were used and the results are presented as mean  $\pm$  standard deviation or in numbers (percent) as appropriate. The significance level was set as  $<0.05$ .

## RESULTS

A total of five patients lost to follow-up; hence, the data of 57 patients were used in the final analysis. The demographic information of the study population is presented in Table-I. A higher percentage of the study population consisted of females (91.2%). Among the patients, 42 individuals (73.7%) had a history of levothyroxine consumption prior to the study.

After 96% ethylic alcohol was injected, the changes were recorded as presented in Table-II. During the follow-up examinations, 54 patients (94.7%) did not show any complications; two patients suffered from regional pain on the nodule during the first week after injection and one patient showed ulceration on the injection site in the first week followed by a scar. After three months, the reduction in nodule size was  $<30\%$  in 21 (36.8%) patients (no response), between 31% and 50% in 9 (15.8%) patients (moderate response), and more than 50% in 27 (47.4%) patients (desirable response); this response

Table-I: Demographic characteristics of the study population.

Sex (N, %)	Male		Female		
	5 (8.8%)		52 (91.2%)		
Age (Years)	Mean ± SD (range) 38.5 ± 10.9 (20-75)				
Age groups (Years)	≤ 40	40 to 49	50 to 59	60 to 69	≥ 70
	37 (64.9%)	14	4	0	2 (3.5%)
Time since nodule formation (months)	Mean ± SD (range) 53 ± 52.4 (6-240)				
Number of nodules (N, %)	Single		Multiple		
	42 (73.7%)		15 (26.3%)		
Nodule size before ethylic alcohol injection (cm³)	Mean ± SD (range) 11.8 ± 9.9 (1.3-50)				

rate was statistically significant ( $P = 0.002$ ). After six months of follow-up, the reduction in nodule size was  $< 30\%$  in 15 (26.3%) patients, between 31% and 50% in 14 (24.6%) patients, and more than 50% in 28 (49.1%) patients; this response rate was also statistically significant ( $P = 0.001$ ). When dividing the patients according to sex and history of levothyroxine use, there was no statistically significant difference among the patients ( $P = 0.31$  and  $P = 0.82$ , respectively). Besides, there was no correlation either between the initial nodule size at the first visit or vascular resistance index and the reduction in their size ( $P = 0.81$  and  $P = 0.16$ , respectively).

## DISCUSSION

In the present study we evaluated the effect of percutaneous ethanol injection (PEI) in the treatment of non-functioning benign solid thyroid nodules in which reduction in nodule volume was considered as the response to the treatment. After 3 months, about 63.2% (36 individuals) of patients showed a reduction of  $>30\%$  among which 47.4% (27) had a reduction of  $>50\%$ ; approximately 73.3% (42) of patients experienced a reduction of  $>30\%$  after 6 months while 49.1% showed a reduction of  $>50\%$  which all were statistically significant.

Several studies have confirmed the effect of PEI in the treatment of thyroid cystic nodules;<sup>8,9,11,12</sup> however its efficacy in thyroid solid nodules is not clear. Some of the studies have reported PEI as a safe effective method in the treatment of thyroid

solid nodules<sup>9</sup> while some others comparing the therapeutic efficacy of PEI in cystic and solid nodules have indicated it as a less effective treatment for solid nodules.<sup>1,13</sup> The probable explanation for this difference is that solid nodules compared with cystic ones are more resistant to be distributed; furthermore, the vascularization of solid nodules leads to faster ethanol drainage from the nodule. These two reasons can influence on the therapeutic efficacy of the procedure in solid nodules<sup>13</sup>; however, in the present study there was no significant relation between the reduction in the nodule size and the vascular resistance index. In a study by Lee et al<sup>9</sup> in which about 88.9% of the patients achieved a nodule reduction of  $>50\%$  by a single PEI, the results strongly indicated that PEI could be an effective treatment for benign solid thyroid nodules; our study showed a similar result but a fewer patients (49.1%) experienced such a reduction. Contrarily, in a study by Filetti et al<sup>1</sup> it was suggested that PEI could be considered as the first-line treatment just for recurrent symptomatic cystic nodules while for other types of nodules only when both surgery and radioactive iodine were contraindicated or unsuccessful, PEI should be considered by assessing the advantages and disadvantages of the procedure for the patient.

In the study evaluating the effectiveness of PEI in benign nodular and cystic thyroid diseases, it was reported that there was a significant relation between the initial and final volumes of the nodule and also between the initial volume and the volume

Table-II: The volume of injected ethylic alcohol and the changes in the nodule size after injection of 96% ethylic alcohol.

Volume of injected ethylic alcohol (cm <sup>3</sup> )	Mean $\pm$ SD (range)	
	6.1 $\pm$ 3.1 (1-10)	
Nodule size after ethylic alcohol injection (cm <sup>3</sup> )	After 3 months	After 6 months
	Mean $\pm$ SD (range) 6.9 $\pm$ 6.6 (0.8-36)	Mean $\pm$ SD (range) 6.4 $\pm$ 6.3 (0.8-36)

reduction of the nodule in which the nodules with a volume of > 10mL significantly showed a greater volume reduction<sup>9</sup>; however, in the present study there was no significant association between the initial volume and the volume reduction of the nodule. The complications of PEI include damage to recurrent laryngeal nerve, local pain, temporary dysphagia and burning sensation.<sup>14,15</sup> Lee et al reported no serious or permanent complication, however transient local pain, as the most common complication of the study, and transient unilateral paralysis of vocal cord were observed in 7.9% and 0.7% of the patients, respectively.<sup>9</sup> In our study, following PEI, 3.5% and 1.8% of the patients respectively experienced pain and a small ulcer which were not present after 3 and 6 months; however, a small scar at the site of PEI was observed in 1.8% of patients after 3 and 6 months.

In a study by Kim et al it was reported that since solid components were more resistant to be distributed, in order to achieve a volume reduction similar to cystic nodules, it would be necessary to perform PEI in several sites of the nodule and inject more ethanol in the nodule which would be accompanied with a greater suffer for the patient and a more complications of the procedure.<sup>13</sup> Besides, in a study evaluating the efficacy of repeating PEI in the treatment of thyroid nodules, it was shown that the efficacy decreased by repeating PEI.<sup>11</sup> Furthermore, Jeong et al reported a higher volume reduction in the cystic thyroid nodules following PEI at the one month follow-up while at the 6-month follow-up there was no significant difference between the different types of the nodule regarding volume reduction.<sup>16</sup> As a result, in the present study, we performed a single PEI for the nodule following the patients for six months. Moreover, the volume of ethanol injection in our study was based on the initial volume of the nodules; therefore larger nodules received a greater ethanol volume and it was not possible to assess the association between the volume of ethanol injection and the volume reduction of the nodule.

### CONCLUSION

PEI therapy can be a safe effective method in the treatment of benign solid thyroid nodules as it is an inexpensive procedure which does not need hospitalization and is performed using available ultrasonic methods. However, it is necessary to conduct more studies with larger sample sizes to compare PEI with other methods which are known as the gold standard treatment for non-functioning benign solid thyroid nodules.

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