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PERCUTANEOUS ETHANOL INJECTION IN BENIGN NONTOXIC MULTINODULAR GOITER

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ABSTRACT

Introduction: Benign non-toxic multinodular goiter is one of the most common endocrine diseases that affect the current population, and it is, in turn, the endocrine disease that most frequently requires surgical intervention.

Objective: To show the results of percutaneous ethanol injection in the treatment of patients with benign non-toxic multinodular goiter in the short and medium term.

Methods: A prospective longitudinal study was conducted in patients with benign nontoxic multinodular goiter treated with percutaneous ethanol injection. The categorical variables were described by absolute frequencies and percentages, and for the numerical variables the mean, standard deviation, as well as the minimum and maximum values were calculated. To evaluate the changes between the initial and final volumes of the nodules, the Student's t-test for related samples was used.

Results: The mean percentage reduction in the volume of the nodules was 48.23 ± 9.55 ; 58.05 ± 11.79 and 69.49 ± 13.11 ; a month, 3 months and 6 months after the treatment, respectively. Clinical success was complete in 67.3%, 75.5%, and 87.8% of the patients, at 1, 3, and 6 months of post-treatment follow-up, respectively. There were no complications.

Conclusions: Percutaneous ethanol injection is an alternative to surgery for the treatment of patients with benign non-toxic multinodular goiter, it is safe, effective, with transient adverse effects and very rare complications in the short and medium term.

Keywords: Goiter, therapy, ethanol.

INTRODUCTION

Multinodular goiter affects more than 650 million people on all continents, representing 4% of the American population and 10% of European populations. Benign non-toxic

multinodular goiter is one of the most common endocrine diseases affecting the current population, and it is, in turn, the endocrine disease that most frequently requires surgical intervention. The symptoms in patients with this diagnosis develop mainly due to the increase in volume of the nodules, which can cause asymmetry of the neck on inspection and manifest only as cosmetic problems, or cause discomfort when swallowing and symptoms of compression. Hyperthyroidism may appear in non-toxic multinodular goiter with years of evolution.⁽¹⁾

There is no consensus on the ideal treatment for patients with this disease. Current alternatives include: clinical follow-up, suppressive therapy with levothyroxine sodium, radioactive iodine therapy, alone or preceded by injection of recombinant human TSH, surgical treatment, and more recently minimally invasive techniques (thermal ablation and chemical ablation).^(1,2)

With the introduction in recent decades of minimally invasive techniques for the treatment of thyroid nodular disease, they have been gaining ground as a safe alternative to surgery in selected patients. As these ultrasound-guided ablation procedures are increasingly used in benign and malignant thyroid disease, thoughtful, evidence-based application of best practices is warranted. Ultrasound-guided ablation procedures can be used as a first-line alternative to surgery for patients with benign thyroid nodules that contribute to compressive symptoms and cosmetic concerns.^(3,4)

Thermal ablation (laser, radiofrequency, microwave, or high-intensity focused ultrasound) as a treatment for thyroid nodular disease (mostly solid nodules) has displaced ethanol ablation, especially in Asian and European countries. Most authors consider that percutaneous ethanol injection (PEI) represents the first line treatment for thyroid cysts and nodules with a predominant liquid component.^(5,6)

The first published experience in the US with the use of ablative techniques in the treatment of benign thyroid nodules was carried out by the Mayo Clinic in 2018.⁽⁶⁾ Currently, in that country, PEI is preferably performed on nodules cystic or predominantly cystic and is considered a prudent option for people with low incomes as it is relatively inexpensive.⁽⁷⁾

In Latin America, studies carried out in countries such as Brazil and Mexico^(5,8) show that PEI, endorsed as a safe and effective alternative for cystic thyroid nodules, is also an effective therapy to reduce solid thyroid nodules of different sizes, hyperfunctioning or not. It is a safe outpatient procedure, without frequent serious complications and with reducing effects of thyroid nodules in the short and long term, it is also an economical treatment and does not require specialized equipment.

In Cuba, a study⁽⁹⁾ conducted at the Dr. “Luis Díaz Soto” Central Military Hospital on the use of PEI in patients with a single thyroid nodule was published in Cuba in 2003. No publications of studies on the use of this therapy in patients with a diagnosis of benign non-toxic multinodular goiter were found in a search carried out with academic Google. Clinical observation, suppressive therapy with levothyroxine sodium (already in decline) and surgical treatment appear to be the only treatment options for patients with this disease.

At the Central Military Hospital "Dr. Carlos J. Finlay" PEI is performed as a first-line alternative to surgical treatment and clinical observation, in patients with symptomatic benign nodular disease or with cosmetic discomfort.

The objective of this research is to show the results of PEI in the treatment of patients with benign non-toxic multinodular goiter in the short and medium term.

METHODS

A longitudinal, prospective study was carried out in patients diagnosed with benign non-toxic multinodular goiter, treated with IPE at the "Dr. Carlos J. Finlay" Central Military Hospital, in the period between November 2021 and July 2022. We worked with the universe of cases, which consisted of 49 patients and 53 nodules, in one patient three nodules were treated and in two patients two nodules were treated.

Inclusion criteria:

- Patients over 18 years of age
- Patients with no family history of thyroid cancer
- Patients with two or more nodules visible on ultrasound, at least one of them with a volume $\geq 6 \text{ cm}^3$
- Patients with negative cytology of malignancy
- Patients with TSH within normal parameters (0.37- 4.7 mUI/L)

Exclusion criteria:

- Patients with a nodule suspected of malignancy
- Patients with symptoms of thyroid hyper function
- Patients who did not accept the procedure.

The variables used in the study were: age (years completed at the time of inclusion in the study), sex (female, male), thyroid hormone value (TSH and T4 value, at the beginning and during the period follow-up), indication for treatment (squeezing symptoms, swallowing discomfort, aesthetic concern), cosmetic score* (1 nodule not palpable or visible, 2 nodule palpable but not visible, 3 nodule visible on swallowing or hyperextension of the neck and 4 nodule visible to the naked eye), nodule type* (solid, $\leq 10\%$ fluid component; predominantly solid, 11-50% fluid component; predominantly cystic, 51-90% fluid component; cystic, $>90\%$ fluid component; and mixed, irregular distribution of the fluid component between the solid zones that makes it difficult to determine the amount), location of the nodule (right lobe, left lobe, isthmus, or a combination of these), size of the nodule* (small, $\leq 10 \text{ cm}^3$, medium, 11 to 30 cm^3 ; large, $>30 \text{ cm}^3$), initial volume (volume of the nodule at the start of treatment), volume at 1 month, 3 months and 6 months (volume of the nodule at 1 month, 3 months and 6 months of treatment), volume reduction percentage* (it was calculated by the formula $V_i - V_f / V_f \times 100$, where V_i is the initial volume and V_f is the final volume), total volume of ethanol (amount of ml of ethanol injected into each nodule) number of sessions (number of times it was performed injection to each nodule), clinical success* (complete, complete resolution of symptoms; partial, improvement of symptoms, but still present; absent, no improvement of symptoms), side effects*: unwanted events that are somewhat expected during or after the procedure (burning, pain, transient

hoarseness, facial edema), minor complications*: A resolves without therapy, without consequences B requires nominal therapy, without hospitalization; major complications*: C requires therapy, minor hospitalization (<48 hours) D requires major therapy, unplanned increase in level of care E prolonged hospitalization (>48 hours).

Variables marked with an asterisk (*) were defined in accordance with the 2019 proposal for standardization of terminology and reporting criteria.⁽¹⁰⁾

The qualitative variables were described by absolute frequencies and percentages, for the numerical variables the average was used, with the standard deviation, as well as the minimum and maximum values. To evaluate the changes between the initial and final volumes of the nodules, the Student's t-test for related samples was used. The data was entered and analyzed in the IBM SPSS 20 program. A reliability level of 95% was used.

ETHICAL CONSIDERATIONS

All the patients included in the study were explained the procedure to be performed, with the possible adverse effects and complications described in the literature. Written informed consent was requested from them, in a model with this detailed explanation and the other treatment options available at the center. The data was only used for research purposes, without revealing the identity of the patients. The research was approved by the ethics committee of the "Dr. Carlos J. Finlay" Central Military Hospital in agreement 9 of 11/25/2021.

DESCRIPTION OF THE TECHNIQUE

For the procedure, a 23 G needle, 5 and 10 ml syringes, 99% ethanol, swabs and Aloka Alpha 5 ultrasound equipment with a 7.5 MHz transducer were used.

The patients were placed in the supine position; a small pillow was placed behind the scapulae to maintain the neck in hyperextension. After skin sterilization, the needle was inserted under ultrasound guidance to the center of the target lesion. In the cystic nodules, predominantly cystic and the predominantly solid ones that allowed it, as much liquid content as possible was aspirated, coupling a syringe to the needle. Once the aspiration was done and keeping the needle in the same location, the aspirated content was evacuated and another syringe with ethanol was connected to it to perform the injection. In solid and mixed nodules, the ethanol injection was performed slowly, moving the needle inside the nodule under ultrasound vision to achieve the most uniform distribution possible throughout the interior of the nodule. Ethanol diffusion through the lesion was monitored as intense echogenicity on real-time observation by ultrasound. In all cases, 30% of the volume of the nodule was injected, estimated by ultrasound before each application, with a maximum limit of 4 ml; the injected ethanol was not aspirated. The percutaneous ethanol injection sessions were performed monthly, after evaluation of the nodular volume by ultrasound and clinical evaluation, the treatment was considered completed when: a) the symptoms or cosmetic discomfort in the patients disappeared; b) the nodular volume was reduced below 6 cm³; c) the consistency, in the case of solid nodules, prevented the injection of ethanol.

For patients with two or more nodules that contributed to the symptoms or cosmetic discomfort that indicated treatment, percutaneous ethanol injection was alternated, with sessions being carried out 15 days apart from one nodule to another.

PEI was performed by the same investigator, experienced in fine-needle aspiration puncture, supported by another investigator, an imaging specialist experienced in ultrasound, who performed all sonographic evaluations.

Telephone communication was maintained with all the patients and they were assessed in a follow-up consultation one month, three and six months after the treatment. At the start of treatment and at each follow-up consultation, each patient underwent evolutionary ultrasound, clinical and hormonal evaluation, and the cosmetic score was applied.

RESULTS

The mean age of the patients included in this study was $47.94 \pm 13,748$, minimum 21 and maximum 82 years. The female sex predominated (79.2%) and the value of TSH and T4 remained at normal levels throughout the follow-up period. The most frequent indication was aesthetic concern, present in 44 patients (83.0%). In 32 patients (60.4%), the location of the treated nodule was the right lobe of the thyroid.

The most frequently treated nodules were mixed (35.8%). Figure 1

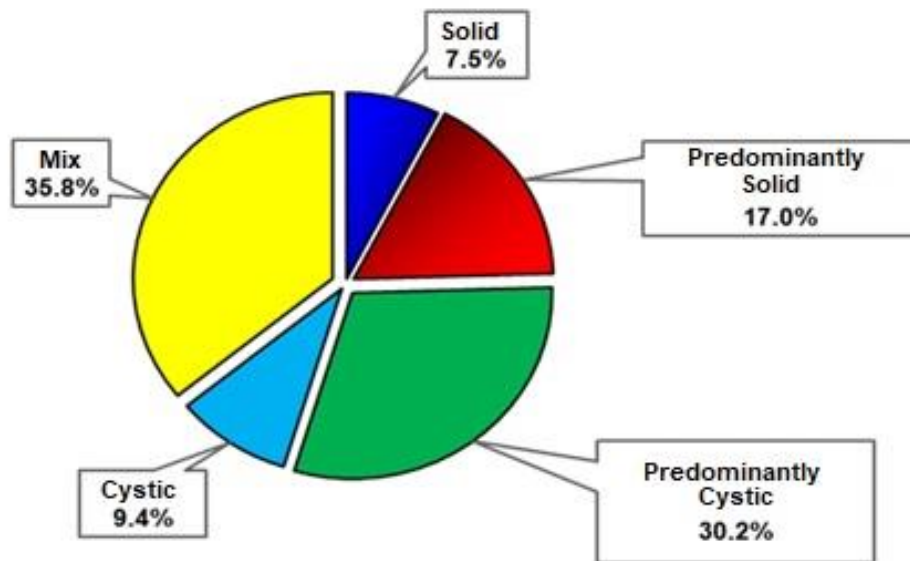


Figure 1. Types of nodules treated in the study

Figure 2 shows the increase in the number of small nodules as the follow-up period progresses, with a decrease in the number of large and medium nodules.

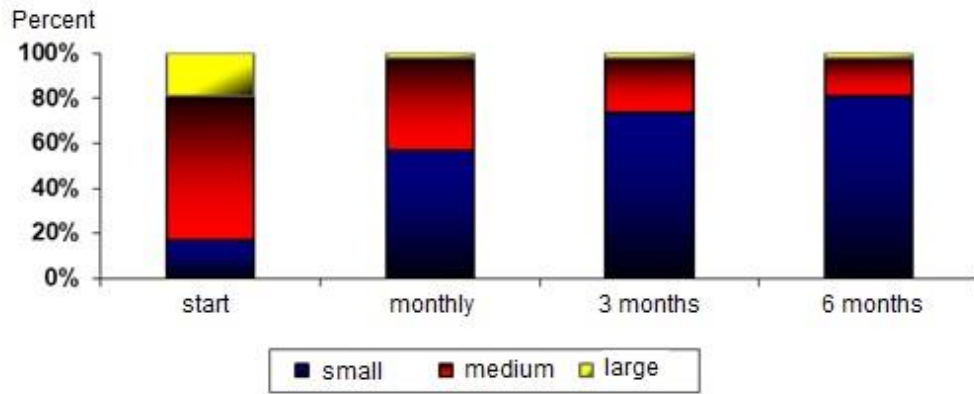


Figure 2. Size of the nodules according to the follow-up period.

The cosmetic score applied to the patients at the beginning of the study and during follow-up visits is shown in Table 1.

Table 1. Cosmetic score applied to patients.

Value	Start		A month		3 months		6 months	
	n	%	n	%	n	%	n	%
0	-	-	-	-	-	-	2	3,8
1	-	-	12	22,6	21	39,6	25	47,2
2	23	43,4	36	68	30	56,6	25	47,2
3	30	56,6	5	9,4	2	3,8	1	1,9
Total	53	100	53	100	53	100	53	100

The mean total volume of ethanol injected into the nodules during treatment was 10.89 ± 8.194 ; minimum 2 and maximum 32 ml. Regarding the number of sessions, it was 2.85 ± 1.985 ; minimum 1 and maximum 8 sessions.

Table 2 shows the variations in the volume of the nodules, before carrying out the treatment (at the beginning) and during the follow-up period at one month, 3 months and 6 months after the treatment. There was a statistically significant reduction in the volume of the nodules ($p < 0.001$).

Table 2. Variation of the volume of the nodules.

Volume	Mean	Standard deviation	Minimum	Maximum
At the beginning	22,5132	14,15850	6,20	93,10
A month	11,5008	7,81500	3,08	57,05
3 months	9,3730	7,28380	0,79	53,58

6 months	6,9594	6,98763	0,51	50,17
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The percentage reduction in the volume of the nodules behaved as follows: mean 48.2272 ± 9.54788 minimum 22.89 and maximum 69.44; mean 58.0470 ± 11.79372 minimum 36.70 and maximum 92.61; mean 69.4891 ± 13.11410 minimum 45.99 and maximum 96.21. One month, 3 months and 6 months after the treatment, respectively.

Clinical success was complete in 67.3%, 75.5%, and 87.8% of the patients, at 1, 3, and 6 months of post-treatment follow-up, respectively. There was no lack of clinical success in any patient. The adverse effects that occurred were burning (24.49%), moderate pain (14.29%) and transient hoarseness (6.12%). There were no complications during the study.

DISCUSSION

The mean age of the patients included in this study was 47.94 ± 13.748 . Ferreira et al.⁽¹¹⁾ report a mean age of 40.4 ± 12.9 and 47 ± 9.5 in patients treated with percutaneous ethanol injection and those who received conservative treatment, respectively. Alcántara-Jones et al.⁽⁵⁾ for their part report a mean age of 50.1 ± 17.4 of the patients with multinodular goiter treated with PEI included in their study. It is suggested that after the age of 40, especially after the age of 60, multinodular goiter is more common.⁽¹⁾

The predominance of the female sex in this research corresponds to the results of other studies.^(11, 8) There is a clear predominance of thyroid disease in the female sex.⁽¹²⁾

The values of TSH and T4 remained within normal limits throughout the study, corresponding to the results shown by other authors who suggest that EPI in cystic and mixed nodules does not interfere with the functioning of the gland, unlike of other types of treatment.^(11, 13) In the present study, no alteration in the functioning of the gland was observed during PEI of solid or predominantly solid nodules.

As stated by Siddappa et al.⁽¹⁴⁾ the main indication for surgery in patients with benign non-toxic multinodular goiter is the aesthetic problem. This corresponds to the most frequent indication presented in this study, since PEI was performed as a alternative to surgical treatment.

Alcántara-Jones et al.^(5, 15) reported the highest frequency of nodules treated in their study, located in the right lobe of the thyroid (41%). In this study, 60.4% of the nodules treated were also located in the right lobe of the gland.

In this investigation, PEI was performed more frequently in mixed nodules (35.8%), while Alcántara-Jones et al.⁽⁵⁾ in their study performed it more frequently in solid nodules (39.1%). Current evidence supports the use of PEI as first-line treatment for pure cysts and predominantly cystic thyroid nodules.^(16,17,18) Solymosi⁽¹⁹⁾ states that current procedures practically do not recommend PEI for solid nodules. with non-autonomous operation, which is surprising because there are publications that report a very good success rate.

The progressive increase in the number of small nodules, during the follow-up period at one month, 3 and 6 months' post-treatment, with the decrease in medium and large nodules, as shown in Figure 2, as well as the improvement in the cosmetic score represented in table 1, show the positive results of the use of PEI for the reduction of the volume of thyroid nodules and the consequent clinical improvement of the patients who receive this treatment. The total volume of ethanol injected, as well as the number of EPI sessions in our study, varies in relation to other studies^(15,19,20) related to this treatment because there is no international consensus regarding the frequency of injection. IPE, the volume of ethanol to be injected in each session, nor the limit of sessions to be carried out.

The variation in the volume of the nodules was statistically significant during the follow-up period, one month, 3 and 6 months after IPE. At the month of follow-up, 28 (52.83%) of the treated nodules had had a volume reduction <50%, only one of them (1.88%) <30%; At 3-month follow-up, 12 (22.64%) of the treated nodules maintained volume reduction <50%, all >30%; and at 6-month follow-up, only 3 (5.66%) of the nodules treated with PEI maintained the volume reduction <50% of the initial volume.

The percentage reduction in the volume of the nodules was 48.23 ± 9.55 , minimum 22.89 and maximum 69.44; 58.05 ± 11.79 minimum 36.70 and maximum 92.61 and 69.49 ± 13.11 minimum 45.99 and maximum 96.21. One month, 3 months and 6 months after the treatment, respectively. Ferreira et al.⁽¹¹⁾ show a rate of nodule volume reduction in their study of 67.7% one month after PEI and 78.2% after a mean of 14 months. Alcántara et al. report a degree of volume reduction of $72.6 \pm 27.3\%$ [mean \pm SD] in nodules treated with IPE. Other studies^(17,21) related to PEI in cystic nodules report volume reduction rates at 6-month follow-up of 84.53 and 94.7%, respectively.

Clinical success in short-term follow-up (1 and 3 months' post IPE) was complete in 67.3% and 75.5% of patients, respectively, while in the medium term (6 months' post IPE) it was complete in 87.8% of the patients. In the rest of the patients, clinical success was partial, and no absence of clinical success was found in any patient during the follow-up period. While in other studies^(5,11) the results of PEI were evaluated according to the reduction in the volume of the treated nodules, in this study the evaluation of the results of PEI was also carried out taking into account the clinical success of the treatment application.

The adverse effects that occurred in this study coincide with the most frequent reported by studies^(5,18,23) related to PEI in any type of nodule. There were no complications.

PEI is an alternative to surgery for the treatment of patients with benign non-toxic multinodular goiter, it is safe, effective, with transient adverse effects and very rare complications in the short and medium term.

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- Conceptualization– Lázaro Lorda Galiano
- Data curation – Lázaro Lorda Galiano, Jacinto Oscar Navas Igarza, Osvaldo Miranda Gómez
- Formal analysis – Lázaro Lorda Galiano, Osvaldo Miranda Gómez
- Research– Lázaro Lorda Galiano, Jacinto Oscar Navas Igarza, Belkis Ortega de la Campa, Henry Pérez López
- Methodology– Lázaro Lorda Galiano, Osvaldo Miranda Gómez
- Project administration – Lázaro Lorda Galiano
- Material resources – Lázaro Lorda Galiano, Jacinto Oscar Navas Igarza, Belkis Ortega de la Campa
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- Visualization– Lázaro Lorda Galiano, Jacinto Oscar Navas Igarza
- Writing– original draft– Lázaro Lorda Galiano
- Writing– review and editing– Lázaro Lorda Galiano, Osvaldo Miranda Gómez
- Writing– review and translating– Lázaro Lorda Galiano, Teresa Lago Alfonso

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DECLARATION OF AVAILABILITY OF RESEARCH DATA

The data set supporting the results of this study is not publicly available.

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