

Cost-minimization analysis of percutaneous ethanol injection treatment of benign solid thyroid nodules: an exploratory pilot study

Análisis de costo-minimización del tratamiento por inyección percutánea con etanol de nódulos tiroideos sólidos benignos: estudio piloto exploratorio

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Abstract

Background: Nodularity in thyroid tissue is extremely common. In Mexico, the only openly available treatment for benign cold thyroid nodules that cause compressive or cosmetic symptoms is surgery. This limitation in the availability of non-invasive treatments places an enormous strain on the State's health resources. **Objective:** To demonstrate the cost-minimization of percutaneous ethanol injection treatment (PEIT) against radiofrequency ablation (RFA) and laser ablation for the treatment of benign solid thyroid nodules. **Method:** Prospective, comparative, quasi-experimental, longitudinal study with external controls, non-randomized, historical, prolective and open. The significant difference in volume reduction was calculated by paired 2-tailed t-test. Validation was made to prove that the reduction in the final nodule volume was non-inferior to the gold standard. The cost-analysis study was carried out using the Montecarlo method. **Results:** 15 patients entered the study. The mean volume of the nodules was 14.46 ± 19 cc, with a final mean volume of 5.24 ± 8.44 cc, the average reduction percentage was $63 \pm 17\%$. The cost per procedure was \$ 18,807 mx, \$ 16,300 mx, \$ 9,248 mx and \$ 1,615 for RFA, surgery, laser ablation and PEIT, respectively. **Conclusions:** The results of the study demonstrate the non-inferiority of the ablation of benign solid thyroid nodules with PEIT compared to laser and RFA, at a lower cost.

Keywords: Nodules. Thyroid. Solid. Ablation. Ethanol.

Resumen

Antecedentes: La nodularidad en el tejido tiroideo es extremadamente común. En México, el único tratamiento disponible abiertamente para los nódulos tiroideos fríos benignos que causan síntomas compresivos o estéticos es la cirugía. This limit in the availability of non-invasive treatments places a huge demand on the health resources of the State. **Objetivo:** Demostrar el costo-minimización del tratamiento por inyección percutánea con etanol (PEIT, percutaneous ethanol injection treatment) contra la ablación por radiofrecuencia (RFA, radiofrequency ablation) y el rayo láser para el tratamiento de nódulos tiroideos sólidos benignos. **Método:** Estudio prospectivo, comparativo, cuasiexperimental, longitudinal, con controles externos, no aleatorizado, histórico, prolectivo y abierto. La diferencia significativa en la reducción de volumen se calculó mediante prueba

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t pareada a dos colas. Se validó que el porcentaje de reducción en el volumen final fue tan eficiente como el método de referencia. El estudio de análisis de costos se realizó utilizando el método de Montecarlo. Resultados: Ingresaron al estudio 15 pacientes. El volumen medio de los nódulos fue de 14.46 ± 19 cc, con un volumen medio final de 5.24 ± 8.44 cc. El porcentaje de reducción medio fue del $63 \pm 17\%$. El costo por procedimiento fue de \$18,807 mx para la RFA, \$16,300 mx para la cirugía, \$9248 mx para la ablación láser y \$1615 mx para el PEIT. Conclusiones: Los resultados del estudio demuestran la no inferioridad de la ablación de nódulos tiroideos sólidos benignos con PEIT en comparación con el rayo láser y la RFA, a un costo inferior.

Palabras clave: Nódulos. Tiroides. Sólidos. Ablación. Etanol.

Introduction

Thyroid nodules are solid or fluid-filled masses formed inside the thyroid tissue. Nodularity in thyroid tissue is extremely common. In Framingham's¹ study, clinically apparent thyroid nodule were present in 6.4% of women and 1.5% of men. The American Thyroid Association states in its guidelines² that routine suppression of the thyroid stimulating hormone with levothyroxine of the benign thyroid nodules in areas with sufficient iodine is not recommended. Treatment of solid thyroid nodules with thermal ablation³, both with RFA (*Radio-frequency Ablation*) and laser, have been very successful³⁻¹⁰, and metaanalysis have even been conducted in order to compare both treatments, and the cost effectiveness of RFA has already been proven against surgery¹¹⁻¹³, but this technology is not openly available in our country, and the cost can be very high. In Mexico, the only openly available treatment for cold thyroid nodules is surgery. This limit in the availability of non-invasive treatments places a huge demand on the health resources of the State. The purpose of this study is to prove that the percutaneous ethanol injection treatment (PEIT) is an effective, efficient, and cost-effective therapeutic option for the treatment of patients with undetectable benign solid thyroid nodules. The therapeutic mechanism of PEIT works by applying ethanol of very high purity (95-99%). Ethanol has several hydrogen bonds in one single molecule and it dissolves rapidly in contact with water. The action mechanism is a combination of two effects: 1) coagulative necrosis of tissues by cell dehydration and denaturing of proteins due to diffusion, and 2) ischemic necrosis due to the formation of blood clots in small blood vessels in the peria-plication tissues, which leads to fibrosis and nodule atrophy. It is believed that the main mechanism is the coagulative necrosis for cystic nodules and ischemic necrosis for solid nodule¹⁴. To the best of our knowledge, the only studies reported with Latin American patients are ours^{15,16} and one study from Brazil¹⁷, which

includes nodule volume reduction data, and there are no studies published in Mexico on the reduction of solid thyroid nodule size (search in PubMed and Cochrane with the terms "PEIT", "ethanol ablation" and "thyroid nodules").

Method

Prospective, comparative, quasi-experimental, longitudinal study with external controls, non-randomized, historical, prospective and open.

Description of the study

The information was gathered from Hospital Ángeles Lomas, in Mexico State, from May 1, 2017 to May 1, 2019. The PEIT was performed guided by ultrasound (MINDRAY 5™). Denatured ethyl alcohol 40B at 99% (JT Baker) was used in all procedures. The total injected volume was calculated at 1 ml of ethanol per ml of nodule volume, divided between three to five sessions, with a maximum ethanol volume applied in a single procedure of 5 ml:

- Less than 5 ml: three sessions.
- Between 5 and 10 ml: four sessions.
- Over 10 ml: five sessions.

Sessions were applied one week apart from each other.

All ultrasounds were performed by the same radiologist, who determined initial, intermediate, and final nodule volumes. All patients had a cytopathology study of the thyroid nodule to be treated. The cytopathology analysis was performed by a team comprised of two cytopathology doctors, and it required them to agree in order to include patients¹⁸.

PEIT procedure

Each participant visited the research facility (suite 345 of Hospital Ángeles Lomas) between three and five

times (depending on the initial nodule volume) in order to perform the procedure in one week intervals (day 0: visit 1; day 7: visit 2; day 14: visit 3; day 21: visit 4; day 28: visit 5), and for three ultrasound follow-up visits (day 44: FU1, day 104: FU2, and day 194: FU3 in case of three ethanol applications; day 51: FU1, day 111: FU2, and day 201: FU3 in case of four ethanol applications; and day 58: FU1, day 118: FU2 and day 208: FU3 in case of five ethanol applications).

Sample calculation

Since this is a pilot study, a minimum of 10 patients was needed.

Eligibility criteria

- Mexican patients of both genders, over the age of 18.
- Patients with benign thyroid nodules (Bethesda II)¹⁸ causing cosmetic or symptomatic issues.
- Patients that visit the office of the main researcher.

Exclusion criteria

- Patients with functional class Bethesda III¹⁸ thyroid nodules or higher.
- Patients with benign thyroid nodules that do not cause cosmetic or symptomatic issues.
- Patients who cannot comply with the ultrasound follow-ups.
- Patients that do not visit the office of the main researcher.

Elimination criteria

- Patients that do not complete the established treatment sessions.
- Patients that decide to leave the study.

Standardization of ultrasound measures

Ultrasounds were conducted exclusively by a radiologist, and the ablation procedure was performed exclusively by the main researcher guided by ultrasound. In order to determine nodule volume, the following equation was used: $V = \pi abc/6$.

The treatment was deemed successful when a volume reduction of > 50% was achieved after 6 months.

Table 1. Demographic patient data

Patient	Age	Sex	Race	Concomitant thyroid conditions
1	47	F	Latina	N
2	42	F	Latina	N
3	44	F	Latina	N
4	43	F	Latina	N
5	20	F	Latina	N
6	57	M	Latina	N
7	36	M	Latina	N
8	46	F	Latina	N
9	43	F	Latina	N
10	46	F	Latina	N
11	54	M	Latina	N
12	64	F	Latina	Y*
13	31	F	Latina	N
14	73	M	Latina	N
15	44	F	Latina	N

F: female; M: male; N: no; Y: yes.

*Patient who had a thyroidectomy with a final diagnosis of thyroid papillary microcarcinoma.

Statistical analysis

A descriptive analysis was conducted expressing data in percentages and mean $\pm$ standard deviation. A significant difference is considered when $p < 0.05$.

The study aims at showing that PEIT at a lower cost is not an inferior treatment¹⁹, and to this end, the variance and measures of central tendency and dispersion were calculated for the different variables. Continuous numerical variables between groups were analyzed by means of Fisher's analysis of variance (ANOVA). The significant difference in volume reduction was established using the two-tail paired t-test. In order to validate the analysis of the accuracy in measuring nodules, an analysis of variance and the coefficient of intraclass correlation ICC2 C1 calculation were used to evaluate the consistency of measurements. In order to understand the possible influence of the observer in measurement errors, the coefficient of intraclass correlation ICC2 A1 was calculated.

Table 2. Nodules characteristics

Patient	Initial volume (cc)	Composition	Functionality	FNA
1	10.89	Solid	Underactive	Benign follicular nodule
2	1.1	Solid	Underactive	Multinodal goiter
3	0.89	Solid	Underactive	Adenomatous nodule
4	8.23	Solid	Underactive	Benign follicular nodule
5	19	Solid	Underactive	Benign follicular nodule
6	1.43	Solid	Underactive	Benign follicular nodule
7	5.2	Solid	Underactive	Benign follicular nodule
8	7.98	Solid	Underactive	Goiter dominant nodule
9	2.6	Solid	Underactive	Adenomatous nodule
10	26.57	Solid	Underactive	Colloid goiter
11	73.47	Solid	Underactive	Benign follicular nodule
12	5.86	Solid	Underactive	Benign follicular nodule
13	11.2	Solid	Underactive	Benign follicular nodule
14	25.16	Solid	Underactive	Benign follicular nodule
15	13.77	Solid	Underactive	Colloid nodule

FNA: fine-needle aspiration biopsy.

The evaluation of concurrent validity was performed by means of the area under the curve calculation, which validated that the percentage of reduction in final thyroid nodule volume was as effective as the preferred method.

The cost-analysis study was carried out using the Montecarlo method.

Table 3. Montecarlo analysis. Comparison of success rate (nodule volume reduction > 50%) and cost per procedure for each of the treatments for non-functional benign thyroid nodules

Treatment	Cost*	Success rate
Surgery	\$17,965	100%
RFA	\$18,807	98.52%
PEI	\$1,615	86.67%
Laser	\$9,248	67%

RFA: radiofrequency ablation; PEI: percutaneous ethanol injection ablation.

*Cost expressed in Mexican pesos.

Ethical considerations

The study strictly complies with the provisions of the General Health Act on Research (LGSMI for its Spanish acronym), with the provisions regarding ethical aspects for research on humans and research biosafety, and goals 1, 2, and 3 of the guidelines of the Joint Commission for the Safety of Participants.

The research project was approved by the local ethics committee and the ethics and research committee of the Bioethics and Health Sciences Faculty of Universidad Anahuac Campus México Norte.

All participants chose to participate willingly and signed the informed consent detailing clearly the procedure and the potential inconveniences, as well as the follow-up to be conducted by the main researcher and research team personnel. Patients were informed of all treatment options available in Mexico and abroad, as well as their cost.

Results

Results in terms of nodule volume reduction and the non inferiority compared to RFA and laser ablation has been previously published¹⁶. A total 15 patients were included in the study, 11 women (73%) and 4 men (27%) with a mean age of 45.93 ± 13.25 years, in a range between 20 and 73 years (Table 1). All patients meet the eligibility criteria with Bethesda II diagnosis, nine with benign follicular nodule (60%), four with adenomatous nodule (27%), and two with non-toxic multinodular goiter (13%) (Table 2). The mean nodule volume was 14.46 ± 19 cc, with a range of 0.809 to 73.47 cc, with a mean final volume of 5.24 ± 8.44 cc, with a range of 0.31 to 34.11 cc. The mean reduction percentage was $63 \pm 17\%$, within a range of 27% to 89% ($p = 0.0055$). Two patients (13.34%) did not complete the study, one of them due to

Table 4. Treatment

Patient	Initial volume (cc)	Final volume (cc)	Number sessions	Reduction percentage	Success	Complications
1	10.89	2.1	4	81	S	1
2	1.1	0.481	3	56	S	n
3	0.89	0.33	3	59	S	n
4	8.23	2.01	4	76	S	n
5	19	7.09	5	63	S	n
6	1.43	0.48	3	66	S	n
7	5.2	1.47	3	72	S	n
8	7.98	3.55	4	56	S	3, 4
9	2.6	0.31	3	88	S	n
10	26.57	2.935	5	89	S	3, 4
11	73.47	34.11	5	54	S	n
12	5.86	5.06	3*	14	N	1
13	11.2	6.89	5 [†]	39	N	2
14	25.16	9.42	5	63	S	n
15	13.77	3.23	5	77	S	n

N: no; Y: yes.

Patient 12 *lost to follow up* (LTFU), last nodule measurement one month after treatment.[†]Patient 13 discontinued treatment after third application due to complications.

1: ethanol extravasation outside the nodule.

2: transient dysphonia.

3: self-limiting hematoma.

4: transient thyroiditis.

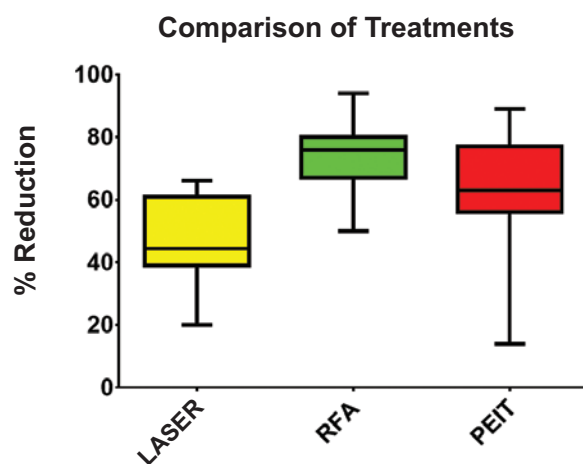


Figure 1. Comparison of nodule volume reduction with laser, radiofrequency (RFA), and ethanol (PEIT). Modified from ref. 16.

complications after three sessions, and another was lost during the follow-up period (6.67%), with only one volume follow-up one month after treatment. Since the study is an *intention to treat* (ITT), we consider

these two patients as treatment failure. Five patients (33%) had complications: ethanol extravasation outside the nodule in two patients, transient dysphonia that required the use of dexamethasone (8 mg) in a patients, self-limiting hematoma in two patients, and transient thyroiditis in two patients (Table 3). Thirteen out of 15 patients (86.67%) achieved a nodule volume reduction of over 50% six months after the last ethanol application. The cost of the procedure was \$18.807 mx for RFA, \$16.300 mx for surgery (hemithyroidectomy with 1 day of hospital stay), \$9.248 mx for laser ablation, and \$1.615 for PEIT; these last three procedures include the use of ultrasound guide. Since patients with hemithyroidectomy can develop hypothyroidism (60% after 5 years), and surgery costs include the potential annual use of levothyroxine as a life-long thyroid replacement therapy (\$1665 mx per year of patient survival) (Table 4).

In order to evaluate the consistency of measurements, the coefficient of intraclass correlation ICC2 calculation was used, and in order to understand the potential observer influence on measurement errors,

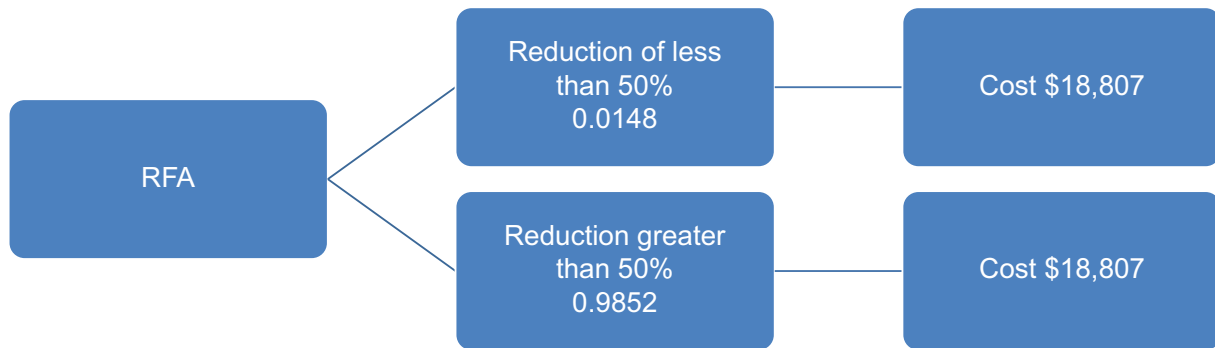


Figure 2. Montecarlo analysis for radiofrequency (RFA) ablation showing a success rate of 98% (nodule volume reduction >50%) with a cost of \$18,807 mx per procedure.

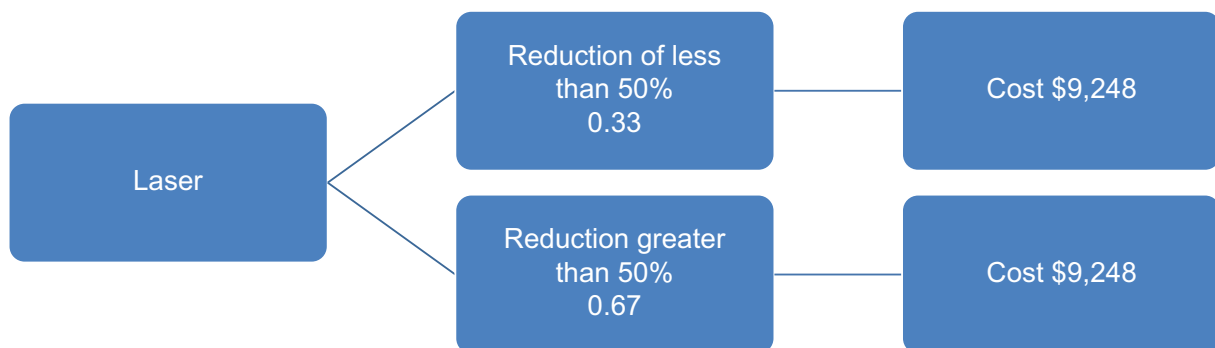


Figure 3. Montecarlo analysis for laser ablation showing a success rate of 67% (nodule volume reduction >50%) with a cost of \$9,248 mx per procedure.

the coefficient of intraclass correlation ICC2 A1 was calculated to quantified absolute agreement, with results of 0.80 and 0.82, respectively. Fisher's ANOVA showed that there was no significant difference between PEIT and RFA in the success rate for nodule volume reduction (Fig. 1), showing a superiority trend between PEIT and laser, and RFA and laser.

The cost-benefit analysis study was performed using the Montecarlo method (Figs. 2 to 5), which showed that surgery has a cost of \$16,300 mx per procedure with a 100% success rate, RFA had a cost of \$18,807 mx per procedure with a success rate of 99%, PEIT had a cost of \$1615 mx per procedure with a success rate of 87%, and laser ablation had a cost of \$9248 per procedure with a success rate of 67%. These costs do not take into account possible expenses derived from procedure complications or the fees for medical staff performing the procedures.

Costs were calculated based on Agreement AS3. HCT.271119/329.P.DF issued by H. Consejo Técnico, during the ordinary session of November 27 of this year, regarding the Approval of Unit Costs per

Level of Medical Care updated in 2020, published by Diario Oficial de la Federación on November 28, 2019.

Discussion

Based on the population data reported previously¹⁹⁻²⁶, we could estimate that, in Mexico, approximately 63 million people could carry one or more thyroid nodules, and around 15 million of them could carry one or more nodules larger than 1 cm. In Mexico, the only openly available treatment for benign cold thyroid nodules that cause compressive or cosmetic symptoms is surgery. PEIT has been used for over 15 years to treat thyroid lesions, both benign and malignant. This procedure can be taught with relative ease (in case of the main researcher, it was done during a 5-day course in the Asan Medical Center in South Korea, in 50 hours of in-person instruction), not only to endocrinology specialists (1784 in 2018), but also to general surgeons (10,982), head and neck surgeons, ENTs (2739), oncology surgeons (3615), and radiologists (3819), which would increase the

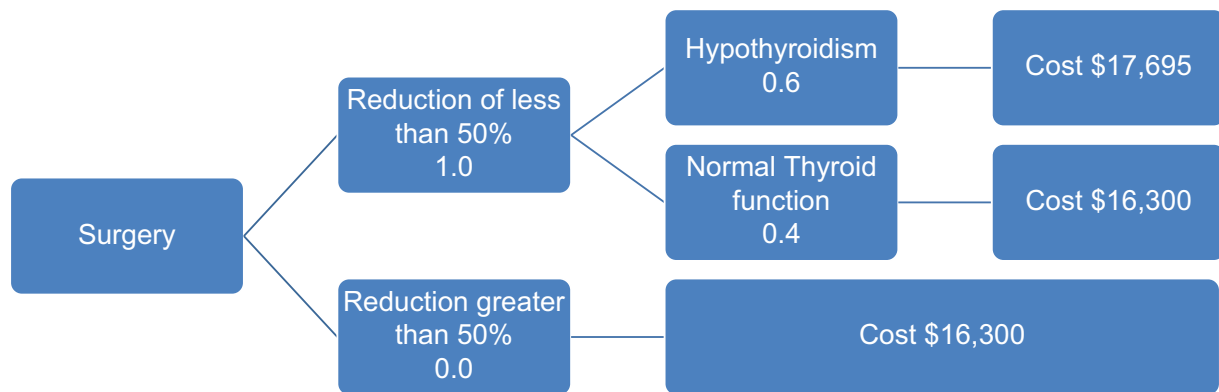


Figure 4. Montecarlo analysis for surgery that shows 100% reduction rate (nodule volume reduction >50%) with a cost of \$16,300 mx per procedure, taking into account that 60% of patients may remain with hypothyroidism, this represents an average of \$1,665 mx per patient survival year.

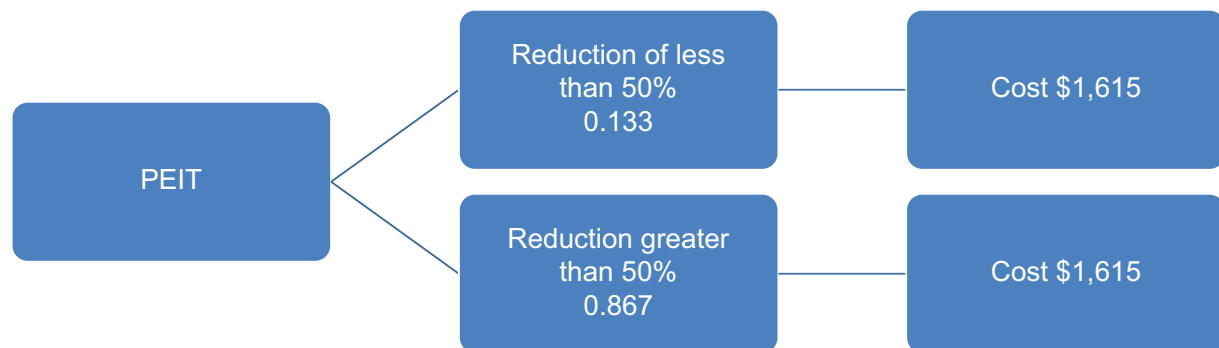


Figure 5. Montecarlo analysis for ethanol ablation (PEIT) showing a success rate of 87% (nodule volume reduction >50%) with a cost of \$1,615 mx per procedure.

number of specialist qualified to treat this pathology from 3615 (4.44 per each 100,000 inhabitants) to 20,200 (24.81 per 100,000 inhabitants)²⁷. The procedure can be performed outside of the OR, with an approximate time of 30 minutes, and it does not require patient hospitalization, which reduces disability days from 10 to 1 day. PEIT opens up the possibility that, in a country with financial and technological limitations as ours, all patients with benign solid thyroid nodules that cause cosmetic or symptomatic alterations can be treated in a medical office, at a very low cost and with a minimum period of disability, which would allow universal access to treatment for these issues. The study aimed at verifying if PEIT is not an inferior treatment compared to RFA and laser, considering a reduction in the initial nodule volume of 50% a success. With this purpose, we first reported volume reduction in our patients and PEIT's success rate, and then, we compared that with the reports in universal literature regarding RFA and laser, because they are not openly available procedures in our country,

we were unable to make an actual comparison of these treatments. Kruskal-Wallis' analysis showed that PEIT was not inferior to RFA and a tendency to superiority of RFA against laser, and PEIT against laser (the purpose of the study was to show that it was not inferior, and therefore, this tendency towards superiority compared to laser will have to be proven in future studies). Our rate of complications is not higher than what has been reported in previous ablation studies with PEIT, or what has been reported in RFA or laser ablation study. The Montecarlo analysis showed cost minimization of PEIT compared to RFA, laser, and surgery.

Conclusions

Our study shows that PEIT achieves a successful reduction in nodule volume with a cost per procedure lower than RFA, laser and surgery, which shows its cost minimization. We believe that PEIT is a safe and underused alternative to surgery in individuals with

benign cold and solid thyroid adenomas. Although it was not part of our initial hypothesis, the results even show a superiority trend of PEIT compared to laser, which must be proven in future studies. This is an exploratory pilot study, and the most limiting part of the study is the sample size, and future studies will require a representative, adequate, and valid sample. The sample size would be calculate with the following²⁸:

$$n = \frac{N\sigma^2 Z^2}{(N-1)e^2 + \sigma^2 Z^2}$$

where n = sample size, N = population size (patients in the office of the main researcher with one or more thyroid nodules) σ = standard deviation of the population (constant value 0.5), Z = level of confidence (1.96 at 95% and 2.58 to 99%) and e = acceptable sampling error limit (between 1 and 9%), which would be:

$$n = \frac{500 \times 0.5^2 \times 1.96^2}{(499 \times 0.09^2) + (0.5^2 \times 1.96^2)} = 96 \text{ patients}$$

Assuming an abandonment rate of 10%, we considered a total of 106 patients.

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Conflicts of interest

The authors declare they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors state that the procedures followed the ethical guidelines of the responsible human experimentation committee and were performed according to the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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