

Evaluation of Ethanol Injection, Radiofrequency Ablation, and Levothyroxine Therapy in the Management of Benign Thyroid Nodules

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Abstract

Background: Thyroid nodules are a common clinical finding. Even though there are various accepted treatments for the benign thyroid nodules, there are alternative methods for managing these patients with fewer expenses and also minimum complications. This study aims to compare the volume decline of radiofrequency (RF) ablation and single-session ethanol ablation (EA) and the effects of levothyroxine therapy for benign thyroid nodule treatment.

Materials: In this clinical trial, 90 patients with benign thyroid nodules in different centers in Tehran, Iran, from December 6, 2018, to December 6, 2019, were included. Patients who had met the inclusion criteria were selected and randomly allocated into three groups (each of 30) of a single session of radiofrequency ablation (Group 1), a single session of ethanol injection (Group 2), or a 6-month LT4 treatment (Group 3). Thyroid tests, including TSH, T4, T3, anti-TPO, T3RU, and serum Calcitonin level, were recorded at baseline and again at 1, 3, and six months. Nodule volume was also assessed through sonography at baseline and the other checkpoints.

Results: The mean volume reduction after 6 months of intervention for ethanol injection group, radiofrequency ablation group, and LT4 treatment group were 72.2%, 83.4%, and 21.8%, respectively. There was a significant relationship between mean volume reduction and months (1, 3, and six) ($P < 0.001$).

Conclusions: Although radiofrequency ablation therapy is the best modality for managing benign thyroid nodules in our study, it is more expensive than the other modalities despite comparable therapeutic effects.

Introduction

Thyroid nodules are a common finding in clinical practice with an incidence of 20–67%, are defined as an isolated lesion of the thyroid gland, which is radiologically different from the surrounding thyroid tissue [1–3]. The prevalence of thyroid nodules grows with age [4]. Most thyroid nodules are clinically insignificant, which are diagnosed incidentally while imaging neck structures are for other reasons, and they can be safely managed with a surveillance program [5]. Diagnostic surgery, Fine-needle aspiration (FNA), and Ultrasonography (US) are different diagnostic methods for screening [6–8].

The management of thyroid nodules is based on the nodule function, local compression symptoms, cosmetic complaints, patient anxiety, and the possibility of malignancy [9–11]. Studies have shown that even thyroid solid nodules diagnosed as a benign lesion in FNA still had a 6% likelihood of being diagnosed as a malignant lesion in surgical pathology [12]. Therefore, dynamic treatments are suggested for suspected thyroid nodules. Several invasive approaches have been introduced for the removal of thyroid nodules. However, these surgical approaches come along with high expenses, permanent scars, and further consequences such as recurrent laryngeal nerve injury, hypocalcemia, hypoparathyroidism, and hemorrhage [13, 14]. Nevertheless, there are some alternatives treatment methods for benign thyroid

nodules, including levothyroxine therapy and minimally invasive treatment methods such as ethanol injection and radiofrequency ablation [15, 16].

This clinical trial study aimed to evaluate benign thyroid nodules' management with ethanol Injection, radiofrequency ablation, and Levothyroxine.

Methods

Study population

This randomized single-blinded clinical trial was conducted on 90 patients with benign thyroid nodules who met our inclusion criteria in different centers in Tehran, Iran. The study protocol was approved by the medical ethics committee of the Gonabad University of Medical Sciences, and all patients provided their informed written consents before inclusion in the study.

The inclusion criteria in our study were: (1) willingness to participate, written consent by patient or family members, (2) aged between 18 to 65 years old, (3) normal thyroid tests including TSH, T4, T3, T3RU, and Anti TPO (4) patients with thyroid nodule, (5) benign thyroid nodules confirmed with FNA under ultrasound, (6) normal calcitonin serum level.

Also, the exclusion criteria were: (1) patients with malignancy findings, (2) patients with malignant or suspicious pathology findings after sonography guided biopsy, (3) pregnancy, (4) abnormal thyroid tests or calcitonin serum level, (5) history of previous treatments related to thyroid nodules.

Research Tools

Patients filled a questionnaire including demographic information, age, sex, weight, height, smoking habits, family history of thyroid cancer, history of cardiac diseases, osteoporosis and menstruation status (for female participants).

Thyroid tests, including TSH, T4, T3, anti-TPO, T3RU, and serum Calcitonin level, were recorded at baseline and again at 1, 3, and six months. TSH (normal range 0.2–4.0 mIU = mL) levels were fixed on an accessible immunoradiometric assay (Sorin Biomedica, Saluggia, Italy). Serum levels of total triiodothyronine (T3, normal range 100–200 ng/mL), thyroxine (T4, normal range 4.6–12 ug/dl), anti-thyroid peroxidase antibodies (TPO-Ab, normal range 0.0–70.0 IU = mL), and calcitonin (normal values < 10 ng/mL) were also fixed on with existing radioimmunologic assay kits (Radim, Pomezia, Italy).

Nodule volume was assessed through sonography at baseline and after 1, 3, and six months.

Randomization and Intervention

In the first step, the aim of the study was explained to participants, and they were asked to fill informed consent. Patients who had met the inclusion criteria were selected and randomly allocated into three groups of a single session of radiofrequency ablation (Group 1), a single session of ethanol injection

(Group 2), or a 6-month LT4 treatment (Group 3). Patients were allocated to one of these three groups using a computer-based number generator. Each patient was assigned a separate code.

Group 1: Radiofrequency ablation (N = 30).

Group 2: Ethanol injection (N = 30).

Group 3: LT4 treatment (N = 30).

A standard dose of LT4 (Euthyrox, Merck, Germany, 1.6–2.1 µg/kg/day to decrease range of TSH levels between 0.1 to 0.4 after 6 months) was administered to the patients assigned to LT4 treatment. According to patients' TSH level, dose was altered at day 35 of experiment. LT4 was amplified if TSH levels > 0.30 mIU = mL and were reduced in patients with unnoticeable TSH or if symptoms of hyperthyroidism were became visible.

Nodule size and volume were examined in all the patients at the baseline of the study and 1, 3, and six months after the intervention. Thyroid nodules volume was estimated using thyroid nodule calculator software and based on the sonography findings at the baseline, 1, 3, and six months after the intervention.

Data Analysis

Data were gathered and analyzed using SPSS 16 statistical software. The normality of the distribution of research variables was examined using the Kolmogorov-Smirnov test. Comparison of nodule volumes in three groups was investigated using the independent t-test. Also, the comparison of before and after intervention for each group was investigated using paired t-test according to the type of variable. The difference between the three groups in terms of demographic variables was determined by independent t-test. Differences with $p < 0.05$ were considered statistically significant.

Results

In this study, among our 90 subjects, 12 patients were men, and 79 patients were women. None of our patients had a history of thyroid cancer or radiation exposure. Six women had a history of cardiac diseases (N = 3) and osteoporosis (N = 3). Also, ten patients were menopausal at the baseline of the study.

The volume reduction percent was calculated for each nodule based on the baseline volume of the nodule, and it was as follow:

In the ethanol injection group, the mean volume reduction at the baseline of the study, 1, 3, and six months after the intervention were 37.4%, 55.6%, and 72.2%, respectively. In the radiofrequency ablation group, the mean volume reduction at the baseline of the study, 1, 3, and six months after the intervention was 46.4%, 64.2%, and 83.4%, respectively. In the LT4 treatment group, the mean volume reduction at the baseline of the study, 1, 3, and six months after the intervention was 18%, 23.6%, and 21.8%, respectively. The highest mean volume reduction was observed in the radiofrequency ablation group, and also the

lowest mean volume reduction was seen in the LT4 treatment group. One way ANOVA test indicated that there was a significant relationship between mean volume reduction and months (1, 3, and six) ($P < 0.001$). There was no significant relationship between age and mean volume reduction in 1, 3, and six months after the intervention (P value = 0.38, 0.73, 0.54; respectively). Also, there was no significant relationship between BMI and mean volume reduction in 1, 3, and six months after the intervention (P value = 0.49, 0.71, 0.94; respectively). Also, the results of this study showed that there wasn't a significant relationship between gender and mean volume reduction in 1, 3, and six months after the intervention (P value = 0.66, 0.72, 0.53; respectively).

Discussion

There are various minimally invasive treatments for benign thyroid nodules, including percutaneous ethanol injection (PEI), radiofrequency, and laser ablation. The former was first performed in 1990 for autonomously functioning thyroid nodules, and it leads to coagulative necrosis and small vessels thrombosis followed by inflammatory changes, consequently result in fibrosis, shrinkage, and volume reduction of the treated zone [16–20].

PEI is the first-line treatment for the relapsing thyroid cyst, and it doesn't need local anesthesia. Significant complications are rare. However, some cases of vocal cord paresis have been reported due to the injection of ethanol outside the cystic cavity. In hyperfunction nodules, the PEI is reported to be associated with a remained risk of hyperthyroidism relapse and progressive regrowth in 70% of patients. Also, the use of PEI in solid thyroid nodules is contraindicated, unless it is the only available treatment [20–24]. According to the studies, PEI in nonfunctioning nodules had been associated with about 50% of nodular volume reduction [25–27]. Consistent with previous studies, in our research, the PEI was associated with the mean volume reduction of 37.4%, 55.6%, and 72.2%, at the baseline of the study, 1, 3 and six months after the intervention, respectively.

The radiofrequency ablation (RFA) was first performed in 2005, and it induces thermal damage followed by coagulative necrosis in the treated zone, leading to nodule shrinkage and fibrosis. Radiofrequency ablation is usually performed under local anesthesia. perithyroidal hemorrhage, recurrent nerve damage, nodule rupture, and skin burns are some of the common consequences which have been reported secondary to the radiofrequency ablation [20, 28]. However, the complication rate is low, and it is reported only in 3.3% of patients [29, 30]. Also, according to the scholars, most of these complications are reversible and go away in long-term follow-ups. According to the studies, radiofrequency ablation has been reported to decrease nodule size by about 50% after six months and by nearly 80%, one year after the intervention [29, 31, 32]. Similar to the previous studies, in our research, in radiofrequency ablation group, the mean volume reduction at the baseline of the study, 1, 3 and six months after the intervention were 46.4%, 64.2%, and 83.4%, respectively. It should also be noted that during the follow-up no complication was observed among our patients.

In a study by Mauri et al., they indicated that percutaneous laser ablation (PLA) and RFA are similarly effective for the treatment of benign thyroid nodules with similar outcome in volume reduction at 1, 6 and 12 months and with the same rate of complications [32].

In a study by Ha et al., they conducted a meta-analysis comparing RFA and PLA for the treatment of thyroid nodules, and they found a 77.8% of mean volume reduction at 6 months in RFA treated group compared with 49.5% in PLA treated group, claiming that RFA seems to be better than PLA in decreasing benign solid thyroid nodule volume [33].

In a randomized trial conducted by Noe Bennedbæk et al., they investigated the effect of percutaneous ethanol injection therapy versus L-thyroxine medical treatment on benign solitary solid cold thyroid nodules, and they concluded that PEI as a single small dose of ethanol is superior to l-T4 suppressive therapy, but is still inferior to surgery [34].

In a prospective randomized study conducted by Yin Huh et al., they investigated the efficacy of additional radiofrequency ablation treatment sessions on symptomatic benign thyroid nodules, and they concluded that a single-session of RF ablation is effective in most patients for improving their cosmetic and symptomatic problems by reducing nodule volume [35].

In a prospective semi-experimental study conducted by Yong Sung et al., on the single-session treatment of benign cystic thyroid nodules with ethanol versus radiofrequency ablation they concluded that both ethanol injection (EA) and RF ablation were helpful and safe treatment modalities, the mean volume reduction of the EA group was non-inferior to and also meaningfully superior to that of the RF ablation group. Therefore, EA could be the leading treatment modality for cystic thyroid nodules, which has equivalent therapeutic efficacy but is more cost-benefit than RF ablation [36].

Our study showed that there is no significant relationship between age, gender, and BMI and mean volume reduction in 1, 3, and six months after the intervention.

Conclusions

To our knowledge, no retrospective semi-experimental study regarding the evaluation of ethanol injection, radiofrequency ablation, and levothyroxine therapy in patients with benign thyroid nodules was conducted before. Our study showed that among these treatments, the radiofrequency ablation was associated with the highest mean volume reduction and also the lowest mean volume reduction was seen in the LT4 treatment group during six months of follow-up. Besides, no complication was observed among our patients.

Abbreviations

FNA: Fine-needle Aspiration; US: Ultrasonography; TSH: Thyroid Stimulating Hormone; T3RU: T3 Resin Uptake; Anti TPO: Anti Thyroid Peroxidase; ANOVA: Analysis of variance; PEI: Percutaneous Ethanol

Injection; RFA: Radiofrequency Ablation; PLA: Percutaneous Laser Ablation; EA: Ethanol Injection; BMI: Body Mass Index; LT4: Long-Term Levothyroxine.

Declarations

Acknowledgments

None

Authors' Contributions

HG provided the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revised it critically for important intellectual content, and final approval of the version to be submitted; AAb: supplied the acquisition of data, drafting of manuscript; AAr: supplied the design of study, analysis and interpretation; MA supplied the acquisition of data; HN.: was responsible for the article critically for important intellectual content; and HH: provided the revised the article critically for important intellectual content and gave final approval of the version to be submitted.

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Availability of data and materials

SPSS data of the participant can be requested from the authors. Please write to the corresponding author if you are interested in such data.

Ethics approval and consent to participate

The ethics committee of Gonabad University of Medical Sciences approved this study. Patients' information was de-identified prior to data analysis and confidentiality of patient information was guaranteed and protected by recording only necessary information regarding this study.

Consent for publication

No individual person's data were included in the manuscript

Competing interests

The authors declare that they have no competing interests

Data availability

The data that support the findings of this study are available from the corresponding authors, upon reasonable request.

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