MedPharmRes

journal of University of Medicine and Pharmacy at Ho Chi Minh City
homepage: http://www.medpharmres.vn/ and http://www.medpharmres.com/

Original article

Efficacy of ethanol ablation for treatment of benign cystic thyroid nodules: the first hospital-based study in Vietnam

Van Bang Nguyen[a*], Van Vy Hau Nguyen[a], Binh Thang Tran[b], Chi Van Le[c]

[a]*Center of Endocrinology and Diabetes, Family Hospital, Da Nang, Vietnam;*
[b]*National Cancer Center Graduate School of Cancer Science and Policy, Goyang, South Korea;*
[c]*Internal Medicine Department, Hue University of Medicine and Pharmacy, Hue University, Hue city, Vietnam.*

Received November 18, 2019: Revised April 06, 2020: Accepted May 12, 2020

Abstract: ***Background:*** In Vietnam, surgery or aspiration is preferred to treat thyroid cysts however each of them still have limitations. Purposes of this study were to evaluate the efficacy and safety of ethanol ablation in treating thyroid cysts and determine factors that predict the outcome of treatment. ***Methods:*** This prospective study was approved by the Ethics Committee of the Institutional Review Board of Family hospital and written informed consent for procedures was obtained. From May 2018 to March 2019, 23 patients who underwent treatment for thyroid cysts by EA were enrolled in this study and were followed up for 1 month at Family hospital. The primary endpoint was efficient after one month as the volume reduction ratio was ≥ 50%. Secondary endpoints were improvements in symptoms, cosmetic scores, and safety. Multiple logistic regression analysis was used. ***Results:*** In the finding, from May 2018 to March 2019, only 17 patients who matched inclusion criteria were included in the analyst, including 7 purely thyroid cysts, and 10 predominantly cystic nodules. Mean volume decreased significantly from 5.21 ± 3.37 ml to 2.35 ± 2.52 ml in corresponding to 52.87% of volume reduction with $p < 0.05$. Ethanol ablation (EA) success rate was 52.90% after 1 month. Symptoms and cosmetic scores were improved significantly. The thyroid function was constant. No adverse events occurred. Purely thyroid cyst was a predictive factor contributing to the success of EA. ***Conclusion:*** EA seems likely to be a safe and an efficient therapy for patients who had purely or predominantly cystic thyroid nodules.

Keywords: Ethanol ablation, cystic thyroid nodules, Vietnam.

1. INTRODUCTION

The thyroid nodule is the second common endocrine disorder behind diabetes [1]. Among thyroid nodules, partially cystic accounted for 53.5 percent, with 13.7 percent described as greater than 75 percent cystic [2]. Once benign nodule has been confirmed, ongoing treatment usually depends on the presence of compressible and/or cosmetic symptoms.

In Vietnam, surgery or aspiration is preferred to treat thyroid cysts but both of them still have limitations such as a scar, general anesthesia, hypothyroidism or high rate of recurrent (50 - 75% of simple aspiration). Ethanol ablation (EA) was used at the end of the 1980s [3]. It destroys tissue permanently by protein degeneration and cellular dehydration, with subsequent necrosis, fibrosis, and thrombosis of small cyst wall blood vessels [4]. In some studies, the success rate after 1 to 3 EA interventions could reach 75 to 85% approximately [5, 6].

*Address correspondence to Van Bang Nguyen at Center of Endocrinology and Diabetes, Family Hospital, Danang, Vietnam; Tel/Fax: (+84) 973445417;
E-mails: Vanbangvnn@gmail.com
DOI: 10.32895/UMP.MPR.4.1.5

EA has been applied for treatment of cystic thyroid nodules at the Da Nang Family Hospital (central of Vietnam) since May 2018. Evaluation of its efficacy and safety has not been conducted yet. Thus, the aim of this study was: To evaluate the efficacy and safety of ethanol ablation in treating benign cystic thyroid nodules and to identify factors that predict the outcome of treatment.

2. METHOD

2.1. Study Design and Patient enrolment

This prospective study was approved by the Ethics Committee of the Institutional Review Board of Family hospital and written informed consent for procedures were obtained from all patients. From May 2018 to March 2019, 23 patients who underwent treatment using ethanol ablation were enrolled in this study. A 1-month follow-up control at Da Nang Family hospital has been conducted for all of them.

Inclusion criteria

Criteria for the patients included in this study are (1) nodules with greater than 50% cystic portion; (2) patients presenting symptoms or cosmetic problems; (3) Normal thyroid function including FT4 and TSH; and (4) cytology confirming benign thyroid nodules after one ultrasound-guided fine needle aspiration (FNA).

Exclusion criteria

Criteria for excluded patients in this study as (1) follicular neoplasm or malignancy findings on ultrasound-guided FNA; (2) current hyperthyroidism; (3) comorbidity of severe diseases with short life expectancy; (4) patients lost to follow-up.

2.2. Efficacy and Safety

The primary endpoint was the efficacy (evaluated by a VRR >50%). Secondary endpoints were improvements in symptoms and cosmetic scores, no change of thyroid function) and safety (defined as no adverse events).

2.2.1. Pre-ablation assessment

Twenty-three patients underwent ultrasound performed by only one radiologist with more than 5 years of experience. Ultrasound-guided FNA examinations were done by a licensed endocrinologist. All investigations were done by a 8 to 12 MHz linear probe of a real-time ultrasound system (Acuson NX2 or NX3, Siemens). Nodule size and internal fluid composition were evaluated on ultrasound and ultrasound-guided FNA. The three diameters of each nodule were measured, and the volume of each thyroid cyst was calculated as: $V = \pi abc/6$ (where V is volume; a, b, c are the 3 diameters), cystic was defined as nodules with <10% solid component, and predominantly cystic was defined as those with 10–50% solid component [7]. Thyroid function was obtained. At enrollment, patients were asked to score their compressive symptoms on a 10 cm scale (0–10). Physicians gave the cosmetic score (1, no palpable mass; 2, a palpable mass but no cosmetic problem; 3, cosmetic problem on swallowing only; 4, readily detected cosmetic problem) [8]. Before treatment of each patient, we explained the advantages and disadvantages of repeat EA.

2.3. Procedure

All the procedures were performed by the same endocrinologist, who has a license certificate, on the outpatient department. Patients underwent the EA procedure in a supine position with mild neck extension. After skin sterilization and local anesthesia with 2% lidocaine at the needle - puncture site, we used an 18 gauge needle to puncture the cyst under ultrasound guidance via the trans-isthmic approach. The maximum volume of internal fluid was aspirated using a 20 ml or 50ml syringe. If the content of the cyst were highly viscous, aspiration was done using a large-bore needle, followed by irrigation with normal saline to remove internal debris and colloid material before ethanol installation. The volume of ethanol injected depended on the amount of aspirated fluid from the cyst, approximately 50 - 70%. After 2 minutes of ethanol retention with the needle in place, the injected ethanol is removed and the needle is withdrawn [4, 9]. Patients were asked to stay in the hospital for 30 – 60 minutes after the procedure.

2.3.1. Follow-up

Follow-up ultrasound, thyroid function tests and clinical examinations were identical to those performed before EA and after 1 month. Treatment efficacy was assessed by measuring the volume reduction ratio (VRR), therapeutic success if VRR >50%. Safety outcomes were reported according to the international working group on image-guided tumor ablation. Major complications included substantial morbidity and disability which increased the level of care resulting in hospital admission, bleeding cases requiring transfusions and permanent voice change cases. Other complications were identified as minor complications (pain, transient voice change…) [10].

$$\text{VRR}\,(\%) = \frac{(\text{Baseline volume} - 1\text{ month posttreatment volume})}{\text{Baseline volume}}\ X\ 100\%$$

2.4. Statistical Analyses

All statistical analyses were performed using SPSS version 20.0 for Windows. Paired t-tests were used to compare changes in nodule volume, symptom score and cosmetic score from before EA to 1 month after EA. The Wilcoxon's matched- pair signed rank test was used to alternate if data cannot be assumed to be normally distributed. Multiple logistic regression analysis was used to determine independent predictors of success (VRR > 50%). Age (continuous variable), sex (categorical variable: male and female), symptom score (continuous variable from 1-10 score), cosmetic score (continuous variable from 1-4 score), initial volume (continuous variable), thyroid functions (TSH, FT4 - continuous variable), volume of fluid aspirated (continuous variable), volume of ethanol injected (continuous variable) and characteristic of cyst (categorical variable: purely thyroid cysts, predominantly cystic nodules) were included in the model. The significance level for all tests was defined as p-value <0.05.

3. RESULTS

3.1. Baseline Characteristics

From May 2018 to March 2019, 23 patients who underwent treatment using EA were enrolled. Through the preliminary findings, only 17 patients validating the inclusion criteria were included in the analysis, including 7 purely thyroid cysts, 10 predominantly cystic nodules. Six patients loss to follow-up with unknown reason.

Table 1 shows the characteristics of the patients. Most of them were female (70.6%). The mean age was 47.35 ± 15.54 years (range 27 - 81). The mean of symptom score and cosmetic score were 6.53 and 3.47, respectively. The volume of ethanol injected was relatively 78.3% of volume fluid aspirated. Most of the color of fluid aspirated was dark bloody (94.1%). Neither major nor minor complications were reported.

Table 1. Baseline characteristics of the patients

Characteristics		n (%)/ Mean ± SD	Min	Max
Age (year)		47.35 ± 15.54	27	81
Sex	Male	5 (29.4%)		
	Female	12 (70.6%)		
Symptom score		6.53 ± 1.46	4	10
Cosmetic score		3.47 ± 0.72	2	4
Volume (ml)		5.21 ± 3.37	1.22	10.78
TSH (microUI/ml)		1.17 ± 0.8	0.11	3.36
FT4 (ng/dl)		1.49 ± 0.42	0.87	2.92
Volume of fluid aspirated (ml)		4.2 ± 2.3	1	10
Volume of ethanol 99,6% injected (ml)		3.29 ± 1.56	1	7
Minor complications		0		
Major complications		0		
Color of fluid aspirated	Dark bloody	16 (94.1%)		
	Yellow	1 (5.9%)		

3.2. Efficacy

Table 2 shows the outcome of volume reduction rate and therapeutic success rate. Mean volume decreased significantly from 5.21 ± 3.37 ml to 2.35 ± 2.52 ml with p < 0.05. This represents approximately 52.87% of the volume reduction ratio after 1 month follow-up. Therapeutic success rates were 52.90%.

Table 2. Volume reduction rate (VRR) and therapeutic success rate (TSR)

Volume (Mean ± SD**),** ml	**Number of patients (n)**	**Value**	**p**
Baseline	17	5.21 ± 3.37	
1-month post-treatment	17	2.35 ± 2.52	<0,05
VRR (%)*	17	52.87	
≥50%	9	52.90	
< 50%	8	47.1	

Therapeutic success rate (TSR) defines as volume reduction rate (VRR) ≥ 50%;

**: statistically significant reduction (p-value<0.05).*

Table 3 presents the clinical outcome after one month treatment. Cosmetics score and symptoms score were significantly reduced with p-value < 0.05. There was no change in thyroid function tests (TSH and FT4 with p-value > 0.05).

Table 3. Comparison of baseline and 1-month post-treatment

Characteristics	Baseline	1 month post-treatment	p-value
Symptom score	6.53 ± 1.46	4.00 ± 1.26	< 0.05
Cosmetic score	3.47 ± 0.72	2.25 ± 0.68	<0.05
TSH (microUI/ml)	1.17 ± 0.8	1.29 ± 0.71	>0.05
FT4 (ng/dl)	1.49 ± 0.42	1.39 ± 1.49	>0.05

3.3. Factors affect to therapeutic success

Table 4 presents the multivariate logistic regression model including gender, age, initial volume of cyst, symptom score, cosmetic score, thyroid cystic profile, volume of fluid aspirated, volume of ethanol 99,6% injected, which showed only purely thyroid cysts was independent predictors of therapeutic success with aOR = 14; 95%CI: 1.13-172.64, p-value <0.05).

Table 4. Multivariate logistic regression analysis of therapeutic success

Variable	aOR	95%CI	p-value
Purely thyroid cyst	14.00	1.13-172.64	<0.05

Multivariate logistics model: adjusted for age, gender; aOR: *adjusted Odd Ratio*

4. DISCUSSION

This prospective study showed a safe and effective profile of EA in treatment of benign thyroid cysts. The cystic volume decreased significantly, from 5.21 ± 3.37 ml to 2.35 ± 2.52 ml. Cosmetic score and symptom score were significantly reduced. There were no changes in thyroid function tests. Mean VRR was 52.87% ± 26.74% at 1-month follow-up. Therapeutic success rates were 52.9%. In addition, regarding safety of EA, there were no adverse event. We found that only purely thyroid cyst was an independent predictor of therapeutic success (by 14 times).

Benign thyroid nodule is a relatively common disease. Among patients with cystic or predominantly cystic nodules that are symptomatic, treatment options include aspiration (highly associated with a high rate of recurrence, up to 80%), surgery, and EA. Surgery has some limitations such as scars, general anesthesia, hypothyroidism.

EA is one of the treatments for cystic thyroid nodules in many countries. Ethanol causes reduction in volume of cystic thyroid nodules by triggering cellular dehydration, protein degeneration, coagulation necrosis, and small vessel thrombosis, leading to reactive fibrosis [4]. For this reason, the 2016 American Thyroid Association guidelines recommended aspiration with or without ethanol ablation may be become as a therapeutic intervention if a cyst is large and symptomatic. Many studies have assessed its efficacy after one month follow-up but the results have been heterogenous. The VRR varied from 31% to 78% at 1-month follow-up. Compressive and cosmetic symptoms were solved significantly [11-14]. This may depend on different instruments, techniques, the volume of ethanol injected and type of thyroid cysts (predominantly cystic nodules, purely cystic nodules). Our study showed an average VRR after 1-month follow-up, compared to the literature. Many studies showed a good gradual progression of VRR within longer follow-up periods, which was approximately 90% at 3 months, 83 - 93% at 6 months, and 85 - 95% at 12 months [5, 14, 15]. The quick decrease of volume within the first month after EA helps to solve the main problems of thyroid cysts, including compressive and cosmetic symptoms. The gradual progress of VRR after 1 month and longer periods confirms the efficacy EA in treatment of benign thyroid cysts.

EA could not remove thyroid cyst as completely or quickly as surgery, but its complication rate was proved to be lower than that of surgery and often mild and transient [4]. Literature proved the safety profile of EA in treatment of thyroid cysts. Many studies showed a trivial prevalence of complications of EA in patients with benign thyroid cysts, which were commonly transient pain and no major complications [4, 6, 16]. In our current study, we found neither mild nor major complications. No complications in this study might be due to strictly applying EA's procedures from consensus statement by the Korean society of thyroid radiology (trans-isthmic approach route, the amount of ethanol injected, an ethanol retention time). A trans-isthmic approach route is recommended to prevent a change in the position of the needle tip and ethanol leakage when the patient swallows or talks. The amount of ethanol injected depends on the amount of aspirated material in the nodule; approximately 50% of the aspirate volume is usually injected. Total retention amount of ethanol is empirically recommended not to exceed 10 mL, even for large-sized nodules. An ethanol retention time of 2 minutes was found to be sufficient [4].

Factors related to the efficacy of EA for benign thyroid cysts are still debatable. Several studies found that the success-related factors of EA include the nature of the cyst itself (proportion of solid portion, vascularity, and initial volume) [17]. Other studies showed that it was more effective on pure cysts than predominantly cystic nodules and other characteristics of baseline nodule size, aspirate, or volume of ethanol injected were found non-significant [11]. In agreement with some previous findings, our study confirmed pure thyroid cyst as a significant factor affecting the VRR. Solid components are more resistant to ethanol and the vascular solid portion can also cause internal bleeding in the nodules during the follow-up period after EA. The difference between our study and several studies about related factors such as initial volume might be due to too small sample size and short time follow-up in our study.

The limitations are the small sample size and the short follow-up time of 1 month. In the design of study, vascularity of cyst was not collected.

In conclusion, these findings show that EA is likely to become the safest and most effective therapy for purely or predominantly cystic thyroid nodules. Nowadays, this less-invasive therapy is becoming popular. Results of our study can be shown to patients looking for alternatives to surgery.

LIST OF ABBREVIATIONS

EA: Ethanol Ablation

FNA: Fine Needle Aspiration

FT4: Free Thyroxin

TSH:Thyrotropin

VRR: Volume Reduction Rate

TSR: Therapeutic Success Rate

SD: Standard deviation

DECLARATIONS

Ethics approval and consent to participate: Written informed consent form was given to patients

Consent for publication: Not applicable

Availability of data and materials: Availability of data and materials supporting our findings will be shared upon request.

Competing interests: Conflict of interest relevant to this article was not reported.

Funding: Not applicable

Authors' contributions: Van Bang Nguyen: designed this study and wrote the preliminary draft of the manuscript. Chi Van Le, Van Vy Hau Nguyen: supervised this project. Binh Thang Tran: critically revised the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank the patients who agreed to participate in this cohort study.

REFERENCES

1. Melmed, S., et al. Nontoxic diffuse and nodular goiter and neoplasia, in Williams Textbook of Endocrinology 12th Edition. Elsevier. 2011;440-78.
2. Douglas, S. Overview of thyroid nodule formation, in Wolters Kluwer. 2017. Uptodate.com.
3. Jayesh, S.R., et al. Efficacy and safety of USG-guided ethanol sclerotherapy in cystic thyroid nodules. The Indian journal of radiology & imaging. 2009;19(3):199-202.
4. Hahn, S.Y., Shin, J.H., et al. Ethanol Ablation of the Thyroid Nodules: 2018 Consensus Statement by the Korean Society of Thyroid Radiology. Korean J Radiol. 2019;20(4):609-20.
5. Valcavi, R. and Frasoldati. A. Ultrasound-guided percutaneous ethanol injection therapy in thyroid cystic nodules. Endocr Pract. 2004;10(3):269-75.

6. Park, H.S., et al. Ethanol ablation as a treatment strategy for benign cystic thyroid nodules: a comparison of the ethanol retention and aspiration techniques. Ultrasonography. 2018.
7. Shin, J.H., et al. Ultrasonography Diagnosis and Imaging-Based Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. Korean J Radiol. 2016;17(3):370-95.
8. Baek, J.H., Kim Y.S., and e. al. Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. AJR Am J Roentgenol. 2010;194(4):1137-42.
9. Park, H.S., Baek J.H., and e. al. Innovative Techniques for Image-Guided Ablation of Benign Thyroid Nodules: Combined Ethanol and Radiofrequency Ablation. Korean J Radiol. 2017;18(3):461-9.
10. Ahmed, M., et al. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. J Vasc Interv Radiol. 2014;25(11):1691-705 e4.
11. Basu, N., et al. Percutaneous ethanol ablation in managing predominantly cystic nodules thyroid nodules: An eastern India perspective. Indian J Endocrinol Metab. 2014;18(5):662-8.
12. Jang, S.W., et al. How to manage the patients with unsatisfactory results after ethanol ablation for thyroid nodules: role of radiofrequency ablation. Eur J Radiol. 2012;81(5):905-10.
13. Lee, J.H., et al. Radiofrequency ablation (RFA) of benign thyroid in patients with incompletely resolved clinical problems after ethanol ablation (EA). World J Surg. 2010;34(7):1488-93.
14. Sung, J.Y., et al. One-step ethanol ablation of viscous cystic thyroid nodules. AJR Am J Roentgenol. 2008;191(6):1730-3.
15. Baek, J.H., Ha E.J., and e. al. Radiofrequency versus Ethanol Ablation for Treating Predominantly Cystic Thyroid Nodules: A Randomized Clinical Trial. Korean J Radiol. 2015;16(6):1332-40.
16. Sung, J.Y., et al. Single-session treatment of benign cystic thyroid nodules with ethanol versus radiofrequency ablation: a prospective randomized study. Radiology. 2013;269(1):293-300.
17. Kim, Y.J., Baek J.H., and e. al. Cystic versus predominantly cystic thyroid nodules: efficacy of ethanol ablation and analysis of related factors. Eur Radiol. 2012;22(7):1573-8.