The American Journal of Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.elsevier.com/locate/amjsurg

Original Research Article

Ethanol ablation for the treatment of benign thyroid nodules

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ARTICLE INFO

Keywords:
Thyroid nodule
Thyroid cyst
Ethanol ablation
Percutaneous ethanol injection

ABSTRACT

Background: Ethanol ablation (EA) is a non-surgical option for the treatment of benign cystic thyroid nodules. This study summarizes our preliminary experience with the efficacy and safety of EA.
Methods: A retrospective analysis was performed of patients undergoing EA for symptomatic, benign, cystic and predominantly cystic (≥75%) thyroid nodules. Baseline nodule volume, cosmetic scores, and symptom scores were assessed, as well as volume reduction ratio (VRR), cosmetic and symptom scores at post-procedure months 1, 3, 6, and 12.
Results: 31 patients underwent an uncomplicated EA for a single cyst with an average volume of 21.3 cc (range: 1.7–101.4 cc). Follow-up was limited by the COVID-19 pandemic. Mean nodule VRRs were 66 ± 20% (1 m, n = 17), 87 ± 15% (3 m, n = 9), 72 ± 20% (6 m, n = 7), and 78% (12 m, n = 3). Mean symptom and cosmetic scores decreased concurrently post-procedure.
Conclusion: EA is a safe, effective option for benign cystic and predominantly cystic thyroid nodules.

1. Introduction

Though not routinely performed in the United States, percutaneous ethanol injection, also known as ethanol ablation (EA), has been described as a safe and effective treatment for benign cystic and predominantly cystic thyroid nodules.[1] Though malignancy may not be a concern in these patients, they can still suffer from significant compressive and cosmetic symptoms depending on the nodule's size and location.

Chemical ablations have historically been used to target focal malignancies when effort must be made to salvage as much of the surrounding tissue as possible, such as hepatocellular carcinoma in patients with cirrhosis.[2] Ethanol as an ablative substance acts by 1) diffusing into cells, dehydrating their cytoplasm and denaturing proteins, leading to coagulation necrosis and 2) entering local vasculature and causing necrosis of the endothelium, which leads to ischemic necrosis.[2] For solid tumors, thermal ablation techniques are now often preferred as it can be difficult to uniformly distribute ethanol throughout the tissue.[2] However, ethanol ablation remains an attractive and cost-effective option for focal, benign, cystic lesions that can be accessed percutaneously.

A recent meta-analysis of over 1500 patients (largely outside of the United States) found an average cumulative volume reduction ratio (VRR) of 85% after EA at 12 months post-procedure and similar therapeutic outcomes compared to radiofrequency ablation (RFA).[1] However, because there is generally no requirement for special generators or electrodes, EA is a more affordable option for the appropriate nodules. As an alternative to more invasive surgical procedures, multiple national and international consensus groups offer EA as a reasonable option for patients with benign, symptomatic cystic or predominantly cystic nodules.[3–5]

Although there is substantial international experience in the published literature on ethanol ablation, there remains a dearth of literature on the use of ethanol ablation for treatment of benign thyroid nodules here in the United States. Here we summarize our preliminary, single-institution experience with the efficacy and safety of EA.

2. Methods

2.1. Patients

An IRB approved, retrospective analysis of patients who had undergone EA at our institution was performed (AAAD4780). EA candidates included patients with symptomatic, benign, cystic or predominantly cystic (≥75%) thyroid nodules. All patients had either

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https://doi.org/10.1016/j.amjsurg.2022.01.029
Received 24 November 2021; Received in revised form 15 January 2022; Accepted 30 January 2022
Available online 1 February 2022

undergone previous fine needle aspiration (FNA) of their cyst demonstrating benign pathology (Bethesda II)[6] or had a simple thyroid cyst on ultrasound. The alternatives of surgery and observation were offered to all patients. Patients who had undergone additional procedures to treat their thyroid nodule, such as radiofrequency ablation, were excluded from our analysis.

2.2. Procedures

Our team consisted of 3 endocrine surgeons, all of whom perform ethanol ablation procedures. The procedures were all performed under ultrasound guidance using a 5–12 mHz probe. The patient was placed in the supine position and prepped and draped in standard surgical fashion. A 1:1 mixture of 1% lidocaine and 0.25% bupivacaine was infiltrated underneath the skin and along the thyroid capsule to achieve an adequate local field block. Using a *trans*-isthmic approach as previously described,[7–9] a 16-gauge needle was inserted into the thyroid cyst, taking care to keep the tip of the needle in the center of the cyst at all times. The cyst fluid was slowly aspirated, then cold saline was used to irrigate and aspirate the cyst until the fluid ran clear. We then irrigated and aspirated with 100% ethanol (200 proof) and finally instilled ethanol, the amount being approximately one-third of the original cyst volume ($\leq$ 10 cc).[10–12] In select cases, medial feeding vascular pedicles were also identified and ablated with ethanol. Patients were counseled to take over-the-counter oral analgesics (acetaminophen or ibuprofen) as needed for post-procedure pain. Our technique largely resembled that described by previous groups, though we did leave ethanol instilled in the cyst[11–13] (as opposed to completely aspirating ethanol after injecting[7–9,14–16]) and we did use local anesthetic[7,8] (as opposed to a single-puncture technique with no local anesthetic[10,12,13,16]).

2.3. Data collection

At the time of EA and in follow-up appointments (scheduled at 1, 3, 6, and 12 months post-procedure), nodule volume was calculated based on 3 axis ultrasound measurements using the ellipsoid formula. Recommended follow-up intervals were the same for all patients. Volume reduction ratio (VRR) was calculated as ((initial volume – current volume)/initial volume)*100. Compressive symptoms were assessed using a 1–10 visual analog scale (1 = no symptoms, 10 = extreme compressive symptoms) and cosmetic symptoms with a 0–3 scale (0 = non-palpable on physical exam, 1 = discernible with palpation, 2 = discernible with extension of the neck, 3 = discernible without extension of the neck). Fluid aspirated from the cyst was classified into one of the following categories based on color and viscous quality, similar to a prior study on EA outcomes: hemorrhagic non-viscous, brownish/rusty non-viscous, yellow/serous non-viscous, serosanguinous, hemorrhagic/rusty viscous, and yellow/serous viscous.[12]

2.4. Statistical analysis

Patient data was collected and stored in electronic form using the secure online platform RedCap (Research Electronic Data Capture). Nodule volume, compressive symptom score, and cosmetic symptom score at each post-procedure timepoint were compared to baseline data using a paired student's t-test. Analyses were conducted with R (R Core Team, 2014) and figures were produced using the package ggplot2 (Wickham, 2009). A two-tailed p-value of <0.05 was considered statistically significant.

3. Results

31 patients underwent a single EA procedure for a cystic thyroid nodule between September 2019 and June 2021. Patient characteristics are summarized in Table 1. Prior to the procedure, 23 of 31 patients had FNA confirming benign pathology (Bethesda II), 2 patients had nondiagnostic FNA results (Bethesda I) which were subsequently repeated and also nondiagnostic, and 6 patients did not have biopsy results available but had simple cysts on sonogram.

Table 1
Patient characteristics.[a].

Variable	Whole Cohort (n = 31)
Age (years)	49.5 ± 18.1 (12–85)
Sex (% female)	87% (27)
Previous Biopsy Results	
Bethesda II (Benign)	74% (23)
Bethesda I (Nondiagnostic)	7% (2)
No results available	19% (6)
Calculated Cyst Volume on U/S (cc)	21.3 ± 15.4 (1.7–101.4)
Follow-up Data Available	61% (19)
Length of follow-up (mo)	5.0 ± 4.1 (1–12)

[a] Data are reported as mean ± SD (range) or percentage (n).

All patients tolerated the procedure well. One patient had immediate voice change and dysphagia to liquids that resolved within 24 h. There were no cases of permanent voice change. No post-operative hematoma or abscess was reported. In-person follow-up visits were significantly impacted by the COVID-19 pandemic, limiting post-procedure data collection. Three patients had a full 12 months of follow-up data available at the time of publication (Table 2) Cyst fluid characteristics are summarized in Table 3.

All patients had significant decreases in overall nodule volume as shown in Fig. 1. Mean calculated VRRs were 66 ± 20% at 1 month (n = 17, $p < 0.0001$), 87 ± 15% at 3 months (n = 9, p = 0.006), 72 ± 20% at 6 months (n = 7, p = 0.002), and 78% (range 43–99%) at 12 months (n = 3, p = 0.215). In addition, all patients experienced a decrease in compressive and cosmetic symptoms. Compressive symptom scores (1–10 scale) decreased from 5.5 ± 2.7 at baseline to 1.8 ± 1.7 at 1 month (n = 17, $p < 0.0001$), 1.3 ± 0.7 at 3 months (n = 9, p = 0.003), 2.1 ± 2.6 at 6 months (n = 7, p = 0.045), and 1 (range 1–1) at 12 months (n = 3, p = 0.013) (Fig. 2). Cosmetic symptom scores (0–3 scale) decreased from 2.5 ± 0.8 at baseline to 1.2 ± 1.1 at 1 month (n = 17, $p < 0.001$), 0.6 ± 0.5 at 3 months (n = 9, $p < 0.0001$), 0.9 ± 0.7 at 6 months (n = 7, p = 0.005), and 1.0 (range 0–2) at 12 months (n = 3, p = 0.074) (Fig. 3).

4. Discussion

Here we have summarized our preliminary single-institution experience with EA in 31 patients with symptomatic, benign, cystic thyroid nodules. We saw no significant adverse effects and the procedure was well tolerated by all patients. Furthermore, all three variables evaluated—nodule size calculated via ultrasound measurements, compressive symptom scores, and cosmetic scores—improved after EA, consistent with prior studies.[1]

These measures improved most dramatically in the first month after treatment, further improved at the 3-month mark, and remained stable at 6 months post-procedure. Three patients had a full 12 months of follow-up. One had a VRR of over 99% with complete resolution of their compressive and cosmetic symptoms. Another had a VRR of 90% with complete resolution of compressive symptoms and improved cosmetic symptoms. The third had a less robust VRR, which we theorize may be attributable to the fact that they had a relatively larger solid component to their nodule. Nodule composition has previously been shown to be a predictor of success in EA; Kim et al. found that cystic (<10% solid) nodules had significantly greater volume reduction compared to nodules that were 10–50% solid.[8] Nonetheless, the decrease in size was still sufficient to improve the symptom and cosmetic scores in this patient considerably.

Our outcomes were similar to those reported in non-American cohorts[7–14,16] as well as one American cohort,[15] which have reported VRRs ranging from approximately 70 - 95% after single[9,14] or multiple[7–13,15,16] ethanol ablation procedures and significant reductions in

Table 2
Outcomes 12 Months after ethanol ablation.[a].

Patient	Pre-Procedure			12 Months Post-Procedure			
	Cyst Volume (cc)	Symptom Score	Cosmetic Score	Cyst Volume (cc)	Symptom Score	Cosmetic Score	VRR
1	36.5	7	3	0.2	1	0	99%
2	8.9	6	3	0.9	1	2	90%
3	16.6	3	5	9.5	1	1	43%

[a] Cyst volume was estimated using the ellipsoid formula based on ultrasound measurements. VRR = volume reduction ratio.

Table 3
Cyst fluid characteristics and volume reduction ratio (VRR).

Cyst Fluid Category	n (time of procedure)	n (with follow up data available)	VRR at last follow up
Hemorrhagic	16	11	71 ± 21%
Brownish/Rusty	5	3	75 ± 31%
Yellow/Serous	2	2	95% (92–99%)
Serosanguinous	3	1	91%
Hemorrhagic/Rusty Colloid	4	3	80 ± 13%
Yellow/Serous Colloid	1	–	–

1 Data are reported as mean ± SD, mean, or mean (range). Missing data are due to some patients not having had a follow-up appointment yet or being unable to attend follow-up appointments, largely due to the COVID-19 pandemic.

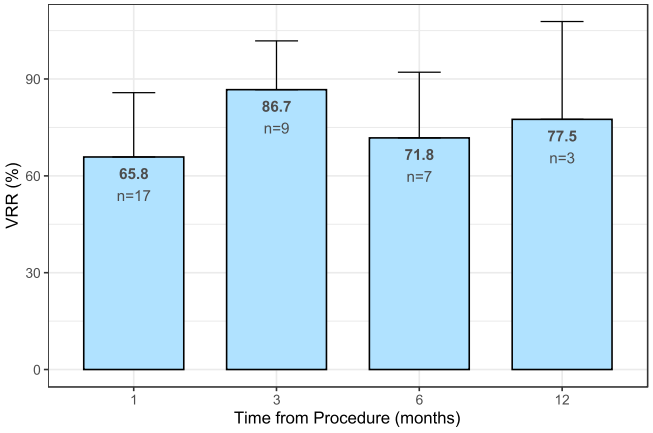

Fig. 1. Thyroid Nodule Volume Reduction Ratio (VRR) After Ethanol Ablation[1].
[1] Mean Volume Reduction Ratio (VRR) at each timepoint in shown in bold. Error bars represent mean + SD.

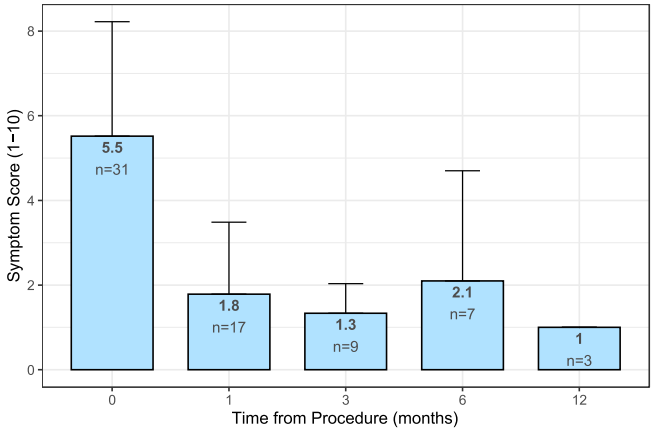

Fig. 2. Compressive Symptom Scores Before and After Ethanol Ablation[1].
[1] Mean symptom score (1–10 scale) at each timepoint is shown in bold. Error bars represent mean + SD. Time 0 = Time of Procedure.

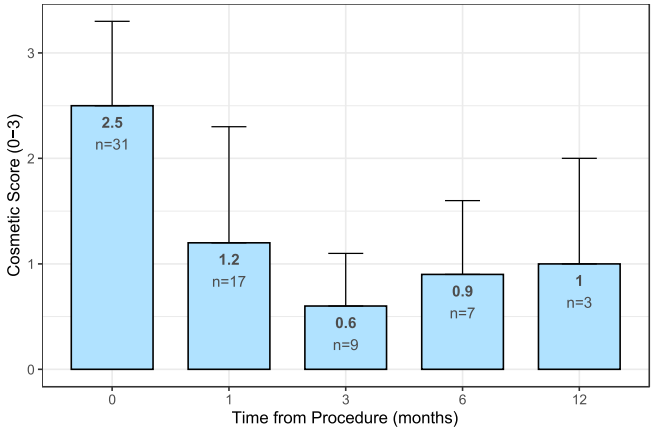

Fig. 3. Cosmetic Scores Before and After Ethanol Ablation[1].
[1] Mean cosmetic score (0–3 scale) at each timepoint is shown in bold. Error bars represent mean + SD. Time 0 = Time of Procedure.

cosmetic and compressive symptoms when measured. The most common complications reported in the literature are occasional cases of transient dysphonia, which we did observe in one out of 31 patients,[7,11,16] and post-procedure discomfort that was adequately controlled with oral analgesics if needed.[8–12,14,15] None of these cohorts reported long term complications, consistent with our preliminary experience.

Although at the time of publication our patients had all undergone a single injection, it should be noted that this procedure is repeatable for those with lingering symptoms due to inadequate volume reduction or returning symptoms due to recurrent growth. Other centers have reported successful volume reduction after 2–3 ethanol injections[7–13,15,16] or more[16] in nodules that did not respond adequately to the initial procedure, without adverse effects. Thus, patients with inadequate relief may still be able to avoid surgery, and some of our patients may be candidates for additional EA procedures in the future.

Our preliminary, single-institution study has several limitations. The office visits that were missed due to the pandemic significantly limited our ability to collect patient data after EA, though the majority of patients still had at least one post-procedure evaluation. Longer-term data and additional patients will warrant further analysis. Our study is strengthened by the fact that we measured multiple variables to evaluate the efficacy of EA, since patient symptoms (both compressive and cosmetic) are equally as important as ultrasound findings in measuring success.

5. Conclusions

EA appears to be a safe and reliable option for benign cystic and predominantly cystic thyroid nodules. Further studies are warranted to evaluate efficacy over longer periods of follow-up.

Funding

No funding to disclose.

References

1. Yang CC, Hsu Y, Liou JY. Efficacy of ethanol ablation for benign thyroid cysts and predominantly cystic nodules: a systematic review and meta-analysis. *Endocrinol Metab (Seoul)*. 2021;36:81–95.
2. Ahmed M, Brace CL, Lee Jr FT, Goldberg SN. Principles of and advances in percutaneous ablation. *Radiology*. 2011;258:351–369.
3. Gharib H, Papini E, Garber JR, et al. American association of clinical endocrinologists, american college of endocrinology, and associazione medici endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules–2016 update. *Endocr Pract*. 2016;22:622–639.
4. Hahn SY, Shin JH, Na DG, et al. Ethanol ablation of the thyroid nodules: 2018 consensus statement by the Korean society of thyroid radiology. *Korean J Radiol*. 2019;20:609–620.
5. Papini E, Monpeyssen H, Frasoldati A, Hegedüs L. European thyroid association clinical practice guideline for the use of image-guided ablation in benign thyroid nodules. *Eur Thyroid J*. 2020;9:172–185, 2020.
6. Cibas ES, Ali SZ. The bethesda system for reporting thyroid cytopathology. *Am J Clin Pathol*. 2009;132:658–665.
7. Baek JH, Ha EJ, Choi YJ, Sung JY, Kim JK, Shong YK. Radiofrequency versus ethanol ablation for treating predominantly cystic thyroid nodules: a randomized clinical trial. *Korean J Radiol*. 2015;16:1332–1340.
8. Kim YJ, Baek JH, Ha EJ, et al. Cystic versus predominantly cystic thyroid nodules: efficacy of ethanol ablation and analysis of related factors. *Eur Radiol*. 2012;22:1573–1578.
9. Sung JY, Baek JH, Kim YS, et al. One-step ethanol ablation of viscous cystic thyroid nodules. *AJR Am J Roentgenol*. 2008;191:1730–1733.
10. Ferreira MC, Piaia C, Cadore AC. Percutaneous ethanol injection versus conservative treatment for benign cystic and mixed thyroid nodules. *Arch Endocrinol Metab*. 2016;60:211–216.
11. Guglielmi R, Pacella CM, Bianchini A, et al. Percutaneous ethanol injection treatment in benign thyroid lesions: role and efficacy. *Thyroid*. 2004;14:125–131.
12. In HS, Kim DW, Choo HJ, Jung SJ, Kang T, Ryu JH. Ethanol ablation of benign thyroid cysts and predominantly cystic thyroid nodules: factors that predict outcome. *Endocrine*. 2014;46:107–113.
13. Jayesh SR, Mehta P, Cherian MP, Ilayaraja V, Gupta P, Venkatesh K. Efficacy and safety of USG-guided ethanol sclerotherapy in cystic thyroid nodules. *Indian J Radiol Imag*. 2009;19:199–202.
14. Gong X, Wang F, Du H, Chen X, Shi B. Comparison of ultrasound-guided percutaneous polidocanol injection versus percutaneous ethanol injection for treatment of benign cystic thyroid nodules. *J Ultrasound Med*. 2018;37:1423–1429.
15. Iñiguez-Ariza NM, Lee RA, Singh-Ospina NM, Stan MN, Castro MR. Ethanol ablation for the treatment of cystic and predominantly cystic thyroid nodules. *Mayo Clin Proc*. 2018;93:1009–1017.
16. Lee SJ, Ahn IM. Effectiveness of percutaneous ethanol injection therapy in benign nodular and cystic thyroid diseases: long-term follow-up experience. *Endocr J*. 2005;52:455–462.