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Efficacy of Ethanol Ablation for Benign Thyroid Cysts and Predominantly Cystic Nodules: A Systematic Review and Meta-Analysis

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Background: Ultrasound-guided minimally invasive procedures are widely used to treat thyroid diseases. The objective of this study was to assess the efficacy and safety of ethanol ablation (EA) in comparison with other non-surgical options in the treatment of benign thyroid cystic nodules.

Methods: We conducted a systematic search of studies on EA for thyroid cystic nodules, mainly in the Ovid-MEDLINE and Embase, Web of Science, and Cochrane databases. The standardized mean difference (SMD) of the volume reduction ratio (VRR) after EA versus other non-surgical treatments comprised the primary outcome, whereas the odds ratio (OR) of therapeutic success rates between the two groups comprised the secondary outcome.

Results: The meta-analysis included 19 studies (four randomized controlled trials and 15 non-randomized studies) with 1,514 participants. The cumulative VRR of EA was 83.908% (95% confidence interval [CI], 79.358% to 88.457%). EA had a significantly higher pooled VRR (SMD, 0.381; 95% CI, 0.028 to 0.734; P=0.030), but not a significantly higher pooled therapeutic success rate (OR, 0.867; 95% CI, 0.132 to 5.689; P=0.880), than other forms of non-surgical management including radiofrequency ablation (RFA), polidocanol sclerotherapy, and simple aspiration with or without saline flush. However, the VRR and therapeutic success rate were not significantly different between EA and RFA. Major complications were recorded only in six patients (0.53%) with self-limiting dysphonia.

Conclusion: The role of EA as the first-line treatment for benign thyroid cysts and predominantly cystic nodules is supported by its high effectiveness and good safety profile compared to other currently available non-surgical options.

Keywords: Ethanol; Ablation techniques; Sclerotherapy; Thyroid nodule; Cyst; Meta-analysis

INTRODUCTION

Thyroid nodules are very common incidental findings, detected in up to 67% of the general population by ultrasonography, and 15% to 25% of thyroid nodules are cystic [1,2]. Around 5% of patients with thyroid nodules may experience compressive symptoms or cosmetic concerns, and treatment may be required in these cases [3]. Simple aspiration is generally the initial management for the purpose of diagnosis and cyst volume reduction. However, the recurrence rate has been reported to be high

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(40% to 59%), depending on the number of aspirations and extent of fluid evacuation [4,5].

Ultrasound-guided percutaneous ethanol ablation (EA) is an effective and safe alternative to surgery in cases of recurrence. The reported volume reduction ratio (VRR) after EA in thyroid cysts (cystic portion >90%) and predominantly cystic thyroid nodules (PCTNs; typically defined as having a cystic portion of 50% to 90%) ranges from 80% to 100% and from 65% to 85.4%, respectively [6-13]. In contrast, the efficacy of EA for treating benign solid thyroid nodules remains controversial, and EA is not recommended in current guidelines for solid nodules [14]. The therapeutic mechanism of EA is a combination of coagulative and ischemic necrosis. The former is caused by direct ethanol toxicity leading to cell dehydration and protein denaturation, while the latter is induced by the entrance of ethanol into the local circulation, resulting in endothelial injury, subsequent thrombosis, and ischemia. Coagulative necrosis is considered to be the predominant effect on cystic lesions [15-17]. Although EA has been proposed as the first-line treatment for relapsing symptomatic cystic thyroid nodules in most guidelines [14,18-22], their recommendations point out a wide range of strengths based on previous reports with heterogeneous quality of evidence. The 2018 consensus statement on EA released by Korean Society of Thyroid Radiology accentuated the role of EA in treating benign thyroid cysts and PCTNs by summarizing more recent high-quality evidence, and further expanded its clinical scope for the management of hyperfunctioning thyroid nodules and local recurrent thyroid carcinoma in selected cases [22].

In recent years, thermal ablation has emerged as a popular non-surgical treatment for benign solid thyroid nodules and recurrent thyroid cancers [21]. In particular, radiofrequency ablation (RFA) has been shown to be effective for treating cystic thyroid nodules [8,10,13,23-26]. The objective of this study was to conduct a comprehensive meta-analysis to compare the efficacy and safety of EA with that of other non-surgical options, including RFA, for the treatment of benign thyroid cystic nodules.

METHODS

Literature search

This meta-analysis adhered to the standard guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Two reviewers (C.C.Y. and Y.H.) independently conducted a systematic search of the databases, including Ovid-MEDLINE and Embase, Web of Science, Cochrane Systematic Reviews, Cochrane Collaboration Central Register of Controlled Clinical Trials, ClinicalTrials.gov and Scopus. Additionally, major Korean medical databases including Korean Medical Article Database, KoreaMed.org, and KoreaMed Synapse were also searched, since most recent studies of EA are from Korea. The search strategy for Ovid-MEDLINE and Embase is presented in Supplemental Table S1. The search was updated to extend through October 2020.

Inclusion criteria

To conform to the population, intervention, comparison, and outcomes (PICO) strategy, our inclusion criteria were set as follows: (1) population: patients with thyroid cysts or PCTNs, for which benignity should be confirmed by fine-needle aspiration; (2) intervention and comparison: two-arm parallel studies comparing EA with other types of non-surgical management, and single-arm studies or case series involving EA with more than 10 participants; and (3) outcome: results reported in sufficient detail to evaluate the VRR (primary outcome, defined as: [final volume–baseline volume]/baseline volume), and therapeutic success rate (secondary outcome, defined as a volume reduction from baseline of more than 50%).

Exclusion criteria

Studies were excluded if any of the following criteria were met: (1) conference abstracts, letters, case series or case reports with fewer than 10 participants; (2) studies not written in English or for which the full text was not available; (3) studies with, or with suspicion of, overlapping populations; (4) studies that either had an arbitrary definition of benign thyroid cystic nodules, or did not enroll those with a cystic portion ≥50% of the nodule volume; and (5) studies that combined EA and other therapies as a whole.

Data extraction

One researcher (C.C.Y.) extracted the data from selected studies, while the other researcher (Y.H.) verified the accuracy. The following data was extracted with a standardized form: (1) mean VRR; (2) therapeutic success rate; (3) the types of nodules and their mean baseline volume; (4) patient demographics, including mean age and sex; (5) technical details, including the volume and concentration of injected ethanol, the retention and aspiration of injected ethanol, and number of treatment sessions; (6) timing of ultrasound follow-up; and (7) minor and major complications, categorized according to the new Society of Interventional Radiology classification [27]. Minor complications

were defined as adverse events without requiring therapy, which were referred to as side effects in this study; major complications were defined as adverse events necessitating substantial therapy, escalation of care, hospitalization, life-threatening morbidity, or even mortality (Table 1).

Quality assessment

Two researchers independently assessed the quality of each included study with scoring systems corresponding to the research methodology. The Cochrane Risk-of-Bias tool 2.0 (RoB 2.0) contains five domains for the identification of potential source of bias in randomized controlled trials (RCTs): the randomization process, deviations from intended interventions, missing outcome data, the measurement of the outcomes, and selection of the reported results [28]. The Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) evaluates the risk of bias in non-randomized studies (NRS) based on six domains: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting [29]. Between-reviewer discrepancies were resolved through discussions under the supervision of the corresponding author.

Statistical synthesis and analysis

The standardized mean difference (SMD) of the VRR between EA and the control group comprised the primary outcome. A positive SMD indicates that EA was the favorable non-surgical treatment option. The effect size was analyzed in terms of the odds ratio (OR) for identifying the therapeutic success rate of EA. An OR >1 indicates that the EA group had a higher success rate than the control group. The inverse variance method and Mantel-Haenszel method were used to estimate the effect size of continuous and dichotomous variables, respectively. Additionally, the generic inverse variance method was employed to pool individual mean VRRs. A random-effects model was used to calculate each overall effect size. Sensitivity analyses, funnel plots and the Egger test were used to examine publication bias. A quantitative synthesis was done using the Cochrane Collaboration's software RevMan 5.4, whereas the Egger test and sensitivity analyses were carried out using Comprehensive Meta-Analysis software version 3 (Biostat, Englewood, NJ, USA). Attempts were made to contact authors for missing data, and the remaining instances of missing data were dealt with reasonable imputation according to the Cochrane Handbook version 6. Between-trial heterogeneity was determined by the inconsistency index (I^2), with values of 25%, 50%, and 75% representing low, moderate, and high degrees of inconsistency or statistical heterogeneity, respectively [30].

RESULTS

Literature search and characteristics of the included studies

A total of 1,772 non-duplicate potentially eligible studies were identified through screening the titles and abstracts, from which 46 articles were retrieved for full text review. The final meta-analysis included 19 studies, consisting of eight two-arm parallel studies (four RCTs [10,11,13,31], two prospective cohort studies [6,32], and two retrospective cohort studies [8,9]), which compared EA with other types of non-surgical management, and 11 single-arm studies (Fig. 1) [7,12,33-41]. Of note, Verde et al. [32] conducted a preliminary RCT followed by a prospective cohort, which was integrated into a larger cohort by pooling the VRRs at 1 month. The characteristics of the included studies are summarized in detail in Table 1.

Characteristics of the ablation techniques

Almost all EA procedures described in the included studies involved subtotal or complete aspiration of the fluid content of cystic nodules prior to ethanol instillation. The injected ethanol was either evacuated (aspiration technique) or retained (retention technique) after the procedure in seven [8-11,13,32,35] and three [31,40,41] studies, respectively. Notably, among studies that enrolled PCTNs, none of them mentioned injection of ethanol into the solid component in addition to filling of the cystic cavity. The procedure was well-tolerated by most participants, with no requirement for local anesthesia. Four trials evaluated the VRR after performing a single session of EA [10,13,32,35], whereas in the other studies, the VRR was assessed after some or all of the participants underwent multiple treatment sessions. The details of the EA techniques in the included studies are also presented in Table 1.

Assessment of study quality

The results of the quality assessment of the four included RCTs according to the RoB 2.0 tool are presented in Fig. 2A, Supplemental Fig. S1A. All four RCTs had a low risk of bias in the domains of deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results. Three of the four studies were considered to have some concerns in the randomization process because the authors did not state allocation concealment [10,13,31], and one of them

Table 1. Demographic Characteristics and Intervention Details of the Included Studies

Study	Nodule type	No. of cases (M/F)	Control management	Study design	Mean age, yr	Baseline nodule volume, mL	EA technique					Ultrasound evaluation, mo	Side effects (*n*)	Major complications (*n*)
							Ethanol concentration, %	Injection, % of cyst volume	Retention, min	Treatment sessions	Local anesthesia			
Sung et al. (2011) [8]	Cyst	EA: 36 (10/26) Control: 21 (3/18)	RFA	RCS	EA: 47.69±13.00 Control: 42.52±10.98	EA: 12.2±11.0 Control: 9.3±11.7	95–99	50	10	Multiple	2% lidocaine	1, 3, 6, 12, last f/u[b]	Mild pain associated with needle puncture	None
Sung et al. (2013) [10]	Cyst	EA: 25 (2/23) Control: 25 (3/22)	RFA	RCT	EA: 45.0±10.9 Control: 44.9±10.6	EA: 13.83±11.97 Control: 10.19±7.01	99	50	10	Single	2% lidocaine	1, 6[b]	Almost no periprocedural pain	None
Baek et al. (2015) [13]	PCTN	EA: 24 (6/18) Control: 22 (3/19)	RFA	RCT	EA: 50.8±15.2 Control: 49.8±13.5	EA: 14.7±13.7 Control: 8.6±9.4	99	50	2	Single	2% lidocaine	1, 6[b]	None	Voice change that spontaneously resolved 2 months later (1)
Gong et al. (2018) [9]	Cyst, PCTN	EA: 135 (50/85) Control: 136 (56/80)	Polidocanol sclerotherapy	RCS	EA: 46.83±11.31 Control: 49.52±11.53	EA: 15.23±18.67 Control: 15.12±19.11	NA	50	10	NA	NA	1, 3, 6, 12[b]	Mild to moderate pain lasting 1–5 days, drunkenness	None
Verde et al. (1994) [32]	Cystic nodules[a]	EA: 42 Control: 10	Simple aspiration	PCS	NA	EA: 20.10±15.40 Control: 26.24±11.37	95	>70	5	Single	None	1[b], 12	Mild self-limiting pain	None
Bennedbaek et al. (2003) [11]	Cyst	EA: 33 (4/29) Control: 33 (7/26)	Isotonic saline flush	RCT	EA: 48 (median) Control: 46 (median)	EA: 8.0±6.7 Control: 8.0±8.1	99	36	2	Multiple	None	1, 2, 3, 6[b]	Transient pain	Transient dysphonia lasting for 1 hour (1)
Valcavi et al. (2004) [31]	Cyst, PCTN	EA: 135 Control: 131	Simple aspiration	RCT	NA	EA: 19.0±19.0 Control: 20.0±13.4	95–100	50–70	No withdrawal	Multiple	None	1, 2, 3, 6, 12[b]	Transient burning sensation, late-onset Local tenderness (begins at 6–8 hours), low-grade fever (rare)	Dysphonia that spontaneously resolved 2 months later (1)
Ferreira et al. (2016) [6]	Cyst, PCTN	EA: 36 (2/34) Control: 13 (0/13)	Conservative (f/u or other non-surgical treatments)	PCS	EA: 40.4±12.9 Control: 47±9.5	EA: 10.4±9.8 Control: 6.2±3.1	99	30	NA	Multiple	None	1 (mean), 14[b] (mean)	Mild pain lingering for 3–4 days, edema	None
Zingrillo et al. (1999) [7]	Cyst	40	None	BA	NA	33.7±25.3	NA	Variable	NA	Multiple	NA	1, 6, 12, 24[b], 36, 48, 60	Transient mild pain	None

(*Continued to the next page*)

Table 1. Continued

Study	Nodule type	No. of cases (M/F)	Control management	Study design	Mean age, yr	Baseline nodule volume, mL	EA technique					Ultrasound evaluation, mo	Side effects (*n*)	Major complications (*n*)
							Ethanol concentration, %	Injection, % of cyst volume	Retention, min	Treatment sessions	Local anesthesia			
Cho et al. (2000) [33]	Cystic nodule[a]	22 (4/18)	None	BA	40.7	13	NA	40–100	NA	Multiple	None	3.5[b] (mean)	Local pain caused by leakage of ethanol into subcutaneous tissue (2)	None
Kim et al. (2003) [12]	Cystic nodule[a]	20	None	BA	NA	15.7	99.90	40–68	NA	Multiple	None	4.4[b] (mean)	Transient pain caused by leakage of ethanol into subcutaneous tissue (4)	None
Guglielmi et al. (2004) [34]	Cystic nodule[a]	58	None	BA	NA	13.7±14.0	95	25	NA	Multiple	None	5[b] years	None	Transient dysphonia (2)[c]
Jang et al. (2012) [35]	Cyst, PCTN	94 (21/73)	EA+RFA	BA	40.4	13.2±15.2	99	50	10	Single	NA	1[b]	Mild pain associated with needle removal	None
Perez et al. (2014) [36]	Cystic nodule[a]	14	None	BA	NA	12.2±12.3	99	33.3	NA	Multiple	None	6 months–11 years	Transient pain caused by leakage of ethanol into subcutaneous tissue	None
Reverter et al. (2015) [41]	Cystic nodule[a]	30 (5/25)	None	BA	46±10	18.2±15.5	99	50	No withdrawal	Multiple	NA	12.1[b] (mean)	Mild pain	None
Negro et al. (2017) [37]	Cyst	101 (30/71)	None	BA	42.3±12.9	14.8±15.5	Absolute ethanol	NA	NA	Multiple	Anesthetic sprayed locally	≤1[b]	Transient mild to moderate pain (21.5%)	None
Espenbetova et al. (2018) [38]	Cystic nodule[a]	75 (3/72)	None	BA	57 (median)	18.4	95	70	NA	Multiple	2% lidocaine	10±1.2[b] years	Transient pain lasting for 1–2 days (1)	Transient dysphonia (1)
Ozderya et al. (2018) [39]	Cyst, PCTN	42	None	BA	NA	15.3±14.0	96	≤20	NA	Multiple	None	1, 3, 6, 12[b]	Transient mild pain at injection site	None

(*Continued to the next page*)

Table 1. Continued

Study	Nodule type	No. of cases (M/F)	Control management	Study design	Mean age, yr	Baseline nodule volume, mL	EA technique					Ultrasound evaluation, mo	Side effects (*n*)	Major complications (*n*)
							Ethanol concentration, %	Injection, % of cyst volume	Retention, min	Treatment sessions	Local anesthesia			
Halenka et al. (2020) [40]	Cystic nodule[a]	193 (43/150)	None	BA	49	8.5 (median)	96	Variable	No withdrawal	Multiple	None	1, 3, 6, 12[b]	Transient mild pain (29%), short-lasting dizziness	Dysphonia spontaneously resolved within 14 days (2)

Values are expressed as mean±standard deviation.
EA, ethanol ablation; RFA, radiofrequency ablation; RCS, retrospective cohort study; f/u, follow-up; RCT, randomized controlled trial; PCTN, predominantly cystic thyroid nodule; PCS, prospective cohort study; NA, not available; BA, uncontrolled before-and-after comparison.
[a]Indicates different definitions of cystic nodules: Reverter et al. (cystic portion >80%); Verde et al. (cystic portion >70%); Cho et al., Kim et al, Espenbetova et al., Halenka et al. (cystic portion >60%); Perez et al. categorized nodules into cystic, mixed, and solid; [b]Indicates the timing of outcome assessment; [c]Indicates that the complication occurred in the parallel group consisting of solid nodules in the same study.

had a significant baseline imbalance in nodule volume and diameter [13]. The results of the methodological assessment of the 15 included NRSs according to the RoBANS are shown in Fig. 2B, Supplemental Fig. S1B. All the studies had a low risk of bias in the domain of selective outcome reporting, whereas most of them had an unclear risk of bias in the domain of blinding of outcome assessments. Six studies had a low risk of bias in the patient selection domain [6-9,35,38], while the others were given an unclear or high risk of bias due to an uncertain process of patient recruitment [12,33,39,41] and retrospective data collection [34,36,37,40] or selection of the intervention and control groups from different populations [32], respectively. One study had high risk of bias in the incomplete data domain due to a large number of dropout cases in long-term follow-up [7]. Additionally, one study had high and unclear risks of bias in the domains of confounding variables and measurement of exposure, respectively, because some of the patients in the control group received an additional suppressive dose of levothyroxine and the potential confounding effect on VRR was not investigated, and because it was not clearly described how exposure data were obtained [6].

Quantitative synthesis (meta-analysis)

Cumulative mean VRR of EA

The cumulative mean VRR of all the included 19 studies was 83.908% (95% confidence interval [CI], 79.358% to 88.457%), irrespective of the timing of ultrasound evaluation and number of treatment sessions. The pooled VRRs at 1, 6, and 12 months were 70.012% (95% CI, 62.620% to 77.404%), 90.754% (95% CI, 84.015% to 97.494%), and 84.966% (95% CI, 79.080% to 90.852%), respectively.

SMD of the VRR between EA and other types of non-surgical management

Overall, eight studies compared the VRR between EA and other non-surgical options [6,8-11,13,31,32]. The pooled SMD of EA versus other types of non-surgical management concerning VRR was 0.381 (95% CI, 0.028 to 0.734; P=0.030; I^2=79%) (Fig. 3A). Subgroup analysis revealed no significant difference between VRR in the EA group and the RFA group (SMD, 0.170; 95% CI, −0.367 to 0.708; P=0.530; I^2=61%), whereas the VRR of EA was significantly higher than that of simple aspiration with or without isotonic saline flush (SMD, 0.716; 95% CI, 0.292 to 1.140; P<0.001; I^2=57%) (Fig. 3A). EA had a similar VRR to that of polidocanol sclerotherapy (SMD, −0.171; 95% CI, −0.410 to 0.068; P=0.160) (Fig. 3A). In the

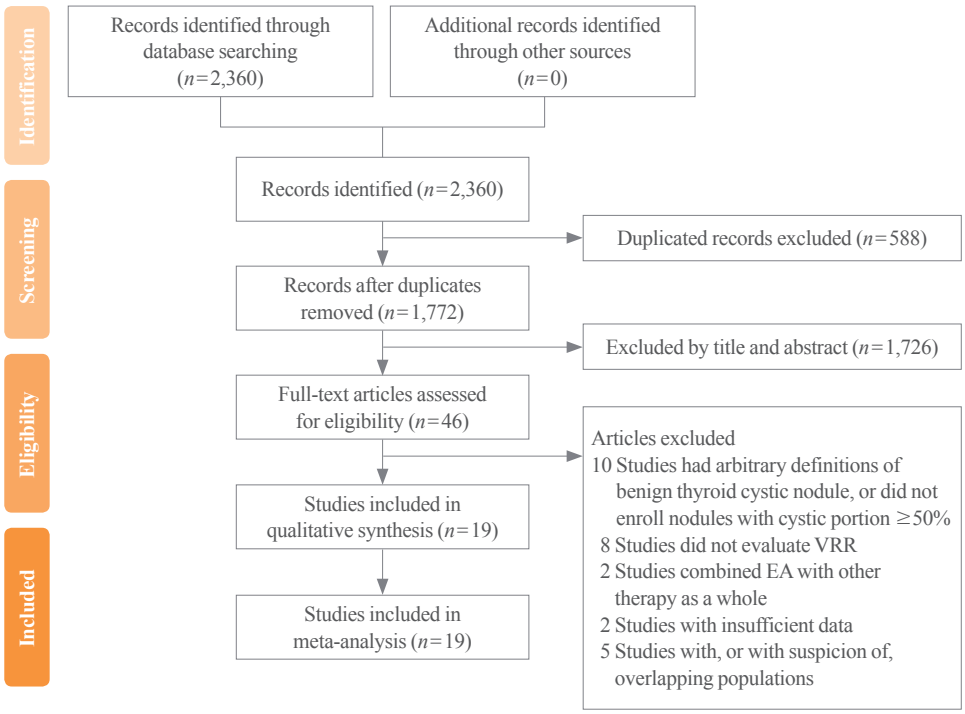


Fig. 1. Flow diagram summarizing the literature review process according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guideline. VRR, volume reduction ratio; EA, ethanol ablation.

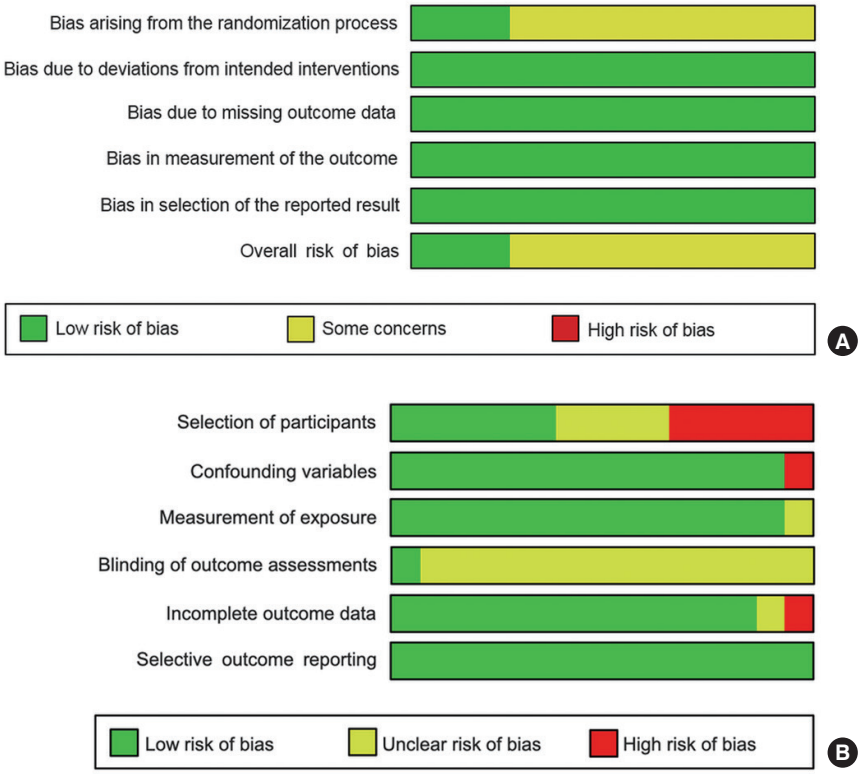
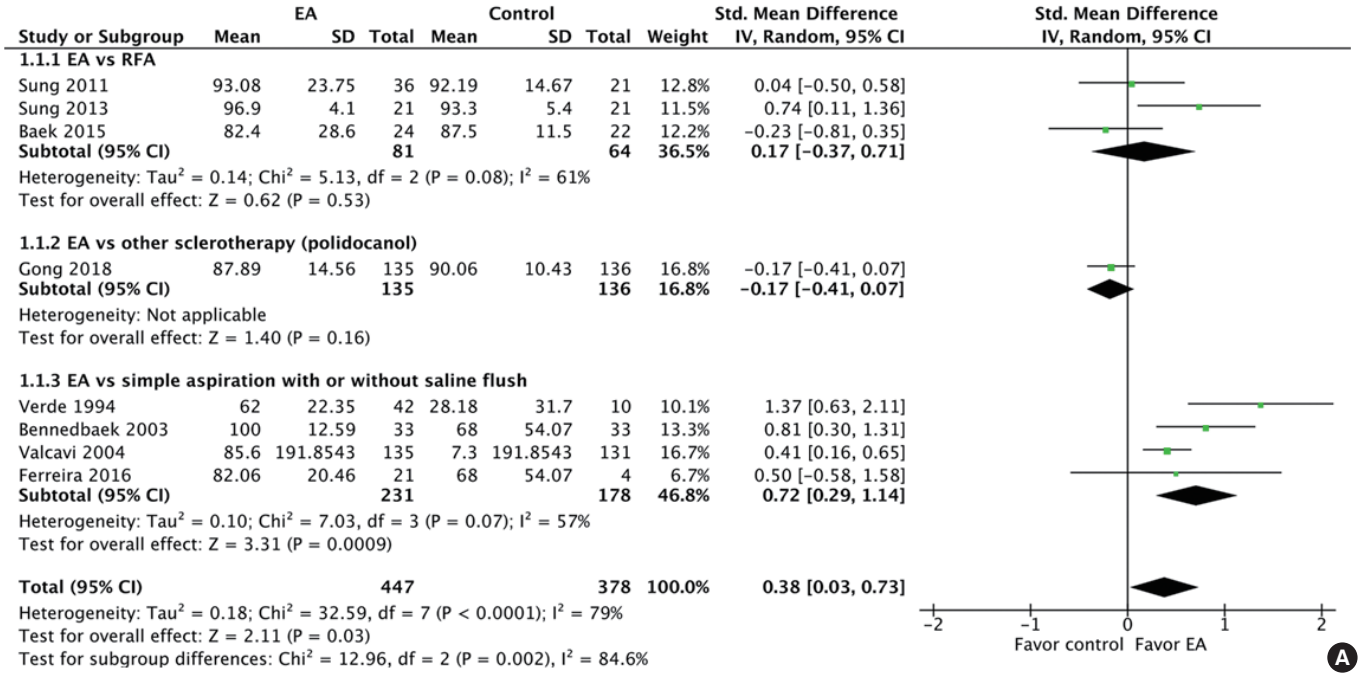


Fig. 2. Summary of quality assessment of the included randomized controlled trials according to Risk-of-Bias tool 2.0 (RoB 2.0) (A), and non-randomized studies according to Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) (B).



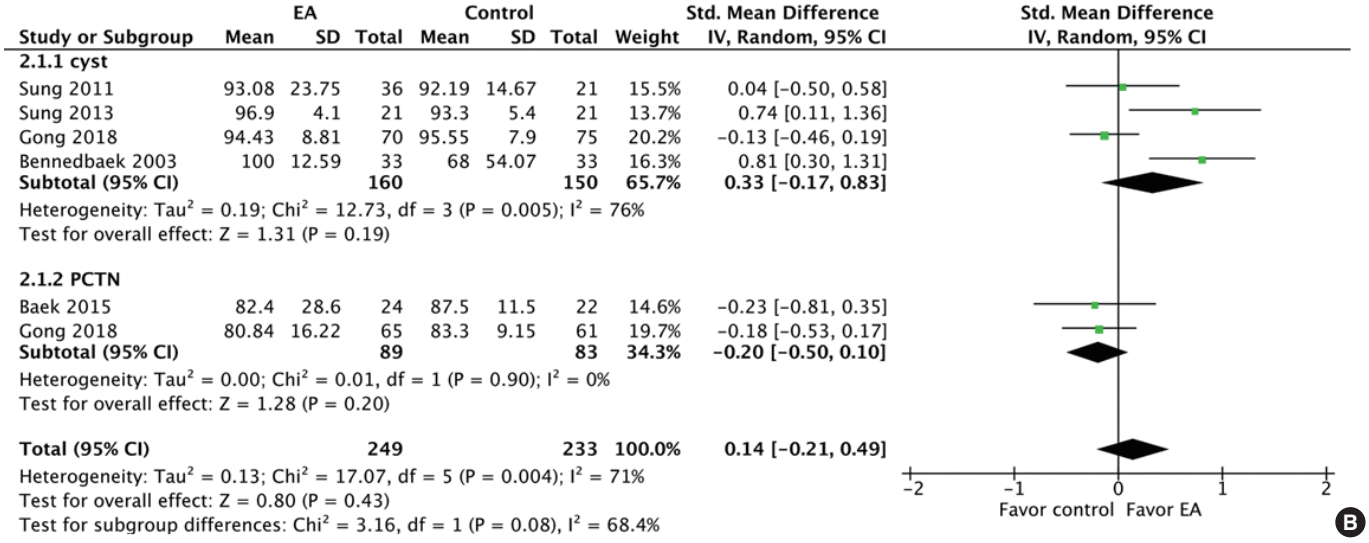


Fig. 3. Forest plots summarizing the efficacy of ethanol ablation (EA) in treating cystic thyroid nodules measured by the volume reduction ratio as compared with other types of non-surgical management, overall effects, and subgroup analysis according to different comparators (A) and cysts versus predominantly cystic thyroid nodules (PCTNs) (B). SD, standard deviation; IV, inverse variance method; CI, confidence interval; RFA, radiofrequency ablation.

subgroup analysis of cysts versus PCTNs, one study [8] compared the two types of nodules separately and was therefore treated as containing two different datasets. Three studies were removed from consideration, including two [6,31] that combined the data of the different types of nodules, and another [32] that enrolled PCTNs with a different definition (cyst content >70%), because the authors believed that it was not reasonable to combine them into either group. Finally, we included six datasets from five studies for this subgroup analysis. As compared with other types of non-surgical management, the VRR after EA was higher in thyroid cysts (SMD, 0.333; 95% CI, −0.166 to 0.832; P=0.190; I^2=76%) but not in PCTNs (SMD, −0.195;

Table 2. Subgroup Analysis of Standardized Mean Difference Based on Study Design, Retention and Aspiration Techniques, and Injected Volume of Ethanol, and Number of Treatment Sessions

Subgroup	Standardized mean difference	95% CI	*P* value	I^2, %
Study design				
RCT	0.434	0.054 to 0.814	0.030	63
NRS	0.364	–0.292 to 1.021	0.280	81
Retention and aspiration of injected ethanol				
Aspiration	0.384	–0.103 to 0.870	0.120	83
Retention	0.407	0.164 to 0.650	0.001	NA
Injected volume				
≥50% of cyst volume	0.300	–0.095 to 0.696	0.140	81
<50% of cyst volume	0.751	0.295 to 1.207	0.001	0
Treatment session				
Single	0.605	–0.304 to 1.514	0.190	83
Multiple	0.428	0.149 to 0.707	0.003	28

CI, confidence interval; RCT, randomized controlled trial; NRS, non-randomized study; NA, not applicable.

95% CI, −0.495 to 0.104; P=0.200; I^2=0%), although neither SMD achieved statistical significance (Fig. 3B). Table 2 presents the results of other subgroup analyses of SMDs based on study design, retention, and aspiration [42], injected ethanol volume, and the number of treatment sessions. Notably, in the subgroups of RCTs and studies that performed multiple treatment sessions, the SMDs of EA were significantly higher than those of the control treatments.

OR of the therapeutic success rate for EA and other types of non-surgical management

Among the eight included parallel studies, five trials [8-10,13, 32] were available for a quantitative analysis of the therapeutic success rate of EA and other non-surgical options. Of note, the therapeutic success rate was 100% in one arm of the study by Baek et al. [13], which was resolved by applying a continuity correction of 0.5 to each cell of the 2×2 table. However, one study was not included in the estimation of the pooled OR by default in the RevMan software because the therapeutic success rate was 100% in both arms [10], as such trials have a small effect on the pooled OR even when they comprise the large majority of included studies [43]. The pooled OR of the therapeutic success rates for EA as compared with other non-surgical managements was 0.867 (95% CI, 0.132 to 5.689; P=0.880; I^2=75%) (Fig. 4A). A subgroup analysis showed no significant differences in the therapeutic success rate between EA and RFA (OR, 0.485; 95% CI, 0.071 to 3.328; P=0.460; I^2=0%) (Fig. 4A). In the subgroup analysis of cysts versus PCTNs, the therapeutic success rate of EA was lower than the control types of management (RFA and polidocanol sclerotherapy) in both cysts and PCTNs ([OR, 0.488; 95% CI, 0.091 to 2.61; P=0.400; I^2=0%] and [OR, 0.269; 95% CI, 0.079 to 0.921; P=0.040; I^2=0%], respectively) (Fig. 4B).

Side effects and major complications

The most common side effect was mild to moderate local pain, which was transient and self-limiting in nearly all cases, without the need for analgesics. Drunkenness was reported to affect a small portion of the participants (10.4%) in one study [9]. Low-grade fever was a rare side effect documented by Valcavi and Frasoldati [31], which spontaneously resolved within 2 to 3 days without medication. Dysphonia was the major complication reported in eight patients from six studies [11,13,31, 34,38,40], with symptom duration ranging from a few minutes to 2 months. Two of the cases complicated by transient dysphonia reported by Guglielmi et al. [34] occurred in the other parallel group consisting of solid nodules, rather than the cystic nodules. Overall, the incidence of self-limiting dysphonia was 0.53% (six of the included 1,136 cases) in patients who underwent EA for benign thyroid cysts and PCTNs.

Sensitivity analysis and publication bias

In the sensitivity analysis (Supplemental Table S2), the quantitative syntheses were repeated after removing one study at a time. Although omitting individual trials did not change the direction of the relationship (favoring EA), the pooled SMD be-

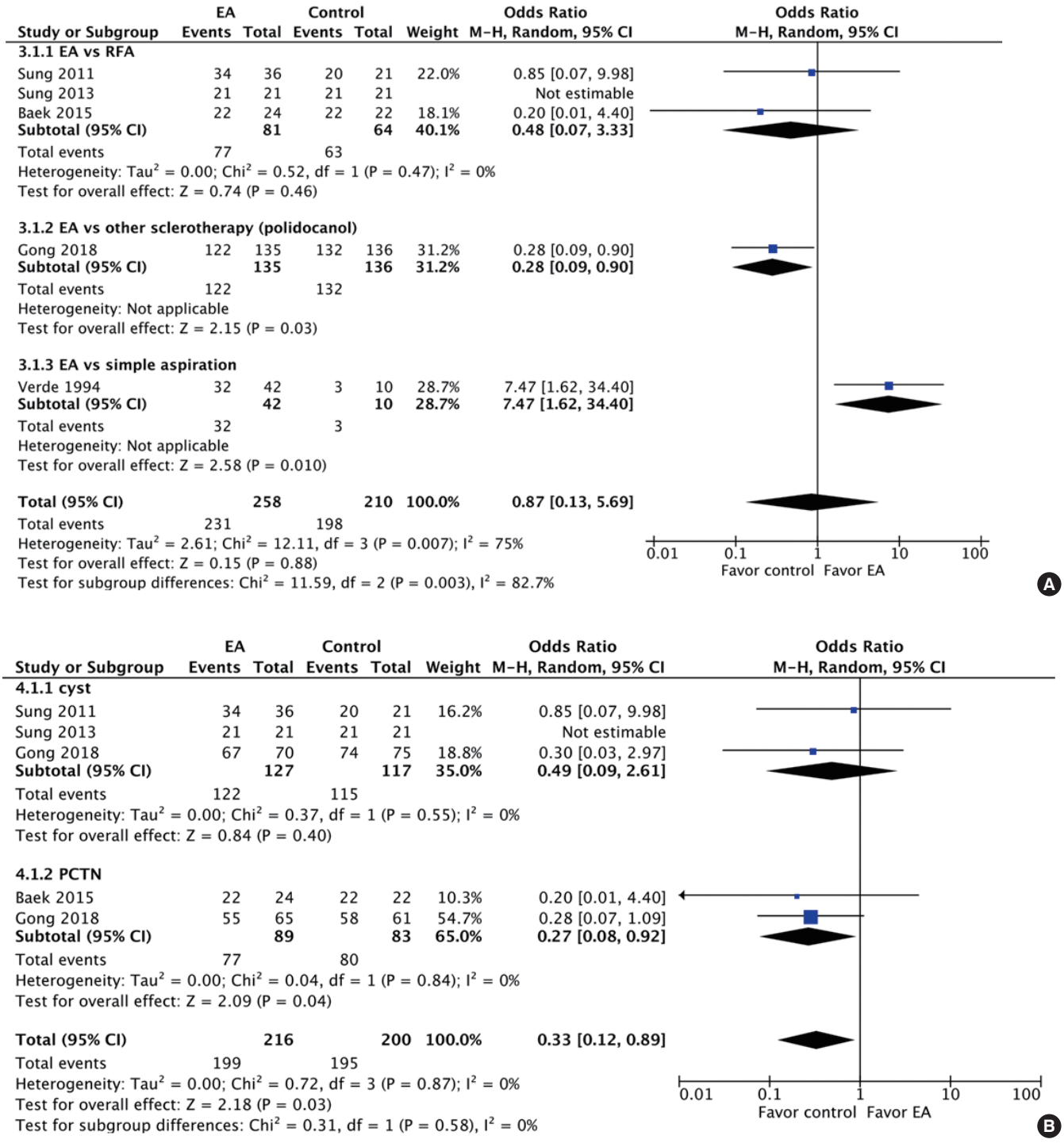


Fig. 4. Forest plots summarizing the therapeutic success rate of ethanol ablation (EA) as compared with other types of non-surgical management, overall effects, and subgroup analysis according to different comparators (A) and cysts versus predominantly cystic thyroid nodules (PCTNs) (B). M-H, Mantel-Haenszel; CI, confidence interval; RFA, radiofrequency ablation.

came statistically insignificant when four individual studies were removed, including most of the studies that compared EA with simple aspiration and saline instillation. The Egger test indicated no significant publication bias regarding the overall SMD (P=0.259). The funnel plot for the SMD of VRR is demonstrated in Fig. 5.

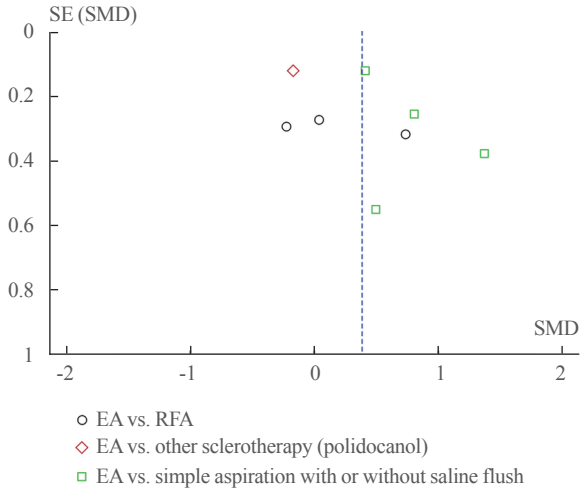


Fig. 5. Funnel plots of studies that evaluated the volume reduction ratio. SE, standard error; SMD, standardized mean difference; EA, ethanol ablation; RFA, radiofrequency ablation.

DISCUSSION

The present meta-analysis compared EA with other non-surgical types of management for the treatment of benign cystic thyroid nodules. Our results indicate that EA and RFA had comparable efficacy in treating cystic thyroid nodules with respect to VRR and the therapeutic success rate. This outcome is consistent with previous reports of high VRRs of RFA in both thyroid cysts and PCTNs (92.2%–93.3% and 83.7%–87.5%, respectively) [8,10,13,44]. However, RFA is more expensive than EA and requires more treatment sessions to have an effect (1.67±0.86 vs. 1.19±0.4, P=0.03). It is also associated with a greater tendency for the patient to experience pain, both during and after the procedure [8,13]. In addition, EA appeared more effective in reducing the volume of thyroid cysts, but not PCTNs, albeit not to a statistically significant degree. These results correspond with the observation of a greater VRR in cysts than in PCTNs after EA from a previous study (89.7% vs. 78.2%, P<0.001) [45]. This can be explained by the conclusion of Kim et al. [12], who suggested that solid components of thyroid nodules are more refractory to EA based on their comparison of EA performed in cystic versus solid nodules. However, only one of the included studies compared EA with another form of sclerotherapy [9]. In fact, a variety of sclerosants in addition to ethanol have been adopted for the treatment of thyroid nodules, including tetracycline, sodium tetradecyl sulfate, N-butyl cyanoacrylate, and polidocanol [46-49]. Among them, polidocanol and sodium tetradecyl sulfate were compared with EA and were shown to have similar VRRs, but higher costs [9,47].

Several factors are known to compromise the efficacy of EA, particularly for PCTNs, including a relatively large initial nodule volume (>20 mL), increased vascularity, a solid portion >20% of the total nodule, and a relatively low degree of cystic fluid aspiration prior to ethanol instillation [35,45,50,51]. Technical factors have also been explored. Kim et al. [52] and Park et al. [42] compared retention and aspiration methods of the injected ethanol and found no significant difference between the two methods in terms of the therapeutic success rate and VRR, respectively. Similarly, different durations of temporary ethanol retention (i.e., 2, 5, and 10 minutes) did not significantly affect the VRR in a study assessing the treatment of cysts and PCTNs [45]. However, our subgroup analysis showed that only studies that performed the retention technique, rather than the aspiration technique, had significantly higher VRRs than other non-surgical options. Nonetheless, Kim et al. [12] demonstrated that a larger injected volume of ethanol was positively correlated with the VRR in thyroid cysts (P<0.01), but not in solid nodules. However, our subgroup analysis showed that EA achieved a significantly higher VRR in the group receiving a lower volume of ethanol instillation (<50% of the initial nodule volume), but not in the group with a higher injection volume. This is because patients in the control arm of the former group received conservative treatment (simple aspiration and saline flush) only. Moreover, the efficacy of EA is also influenced by the number of treatment sessions. Negro et al. [37] reported that the VRRs in thyroid cysts after the first, second, and third EA sessions were 66%, 74.4%, and 79.4%, respectively. Our subgroup analysis also showed that only studies that performed more than one session of EA in some or all of the patients demonstrated a significantly higher pooled VRR than the control management. Although the cure rate varied substantially across studies due to different definitions and numbers of interventions, Bennedbaek and Hegedus [11] reported a 64% cure rate (strictly defined as residual cyst volume ≤1 mL) after a single session of EA in thyroid cysts. Furthermore, the long-term efficacy of EA for cystic thyroid nodules is satisfactory, although long-term results were reported in just a few studies. The VRRs at 2, 3, 5, and 10 years of follow-up in different studies were 72.7%–91.9%, 73.2%–95.8%, 86.6%–98.5%, and 70.2%–100%, respectively [7,34,38,53,54]. The reported recurrence rates in thyroid cysts after EA were low (3.1%–18%), and also varied according to the criteria that were used [11,32,55]. However, in a more recent study of PCTNs, the 1-month recurrence rate was 18.7%, whereas delayed recurrence (mean, 10.1±8.5 months) occurred

in 24.1% of patients who initially did not show recurrence at 1 month of follow-up [51]. When faced with unsatisfactory results after EA, current guidelines [19,21] recommend performing subsequent RFA based on previous studies reporting that significant reductions in nodule volume and improvements in symptomatic and cosmetic problems were achieved after this combination therapy [35,56]. Similarly, for incomplete ablation of solid nodules adjacent to critical structures after RFA, introducing EA as an adjunct technique was shown to be an effective way to eliminate the residual solid component [57,58].

EA is a safe procedure that is well-tolerated by most patients with benign thyroid cysts and PCTNs, with overall side effects that are mild and a considerably low incidence of major complications (self-limiting dysphonia, 0.53%). In contrast, dysphonia was reported in 15 of 1,459 patients (1.0%) who underwent RFA for benign thyroid nodules of unspecified morphological types in a large Korean multicenter study [59]. To our knowledge, permanent dysphonia after EA as a result of recurrent laryngeal nerve injury has never been reported, although severe necrosis of the skin and larynx without irreversible dysphonia was reported in one case involving treatment of a solid nodule [60]. Unlike with thermal ablation, the ablative effect of ethanol is limited to the nodule; therefore, EA does not disrupt thyroid function [6,32,39]. Moreover, local anesthesia was not required in most EA procedures. Notwithstanding its good safety profile, concerns can arise during the follow-up of patients treated with EA, as more than half of the remnant sclerosed nodules may mimic malignancy on ultrasound (i.e., marked hypoechogenicity), leading to unnecessary biopsies [61,62].

The present meta-analysis has some limitations. First, although several studies have assessed EA for the treatment of thyroid diseases, only a few trials have compared EA with other therapies. This fact limited the size of the current meta-analysis. Second, substantial heterogeneity was found with respect to the pooled VRR and therapeutic success rate of EA versus other non-surgical managements. We performed sensitivity analyses, and the pooled VRRs did not reach statistical significance if most studies involving conservative treatment as a comparator were omitted. Therefore, the results of this investigation should be interpreted with caution. More high-quality RCTs comparing EA with other minimally invasive procedures are needed. Third, changes in symptomatic and cosmetic parameters could not be pooled due to a lack of standardized effect size. However, they were shown to parallel the VRR in four included studies [8-10,13] performed using the same scales. Lastly, novel thermal ablative techniques using technologies such as microwave, laser, and high-intensity focused ultrasound have been implemented in recent years to treat thyroid disease. Future research should compare EA with these new treatment options.

In conclusion, EA achieved a higher pooled VRR than other types of non-surgical management and appears to be more effective in the treatment of thyroid cysts than PCTNs. Although RFA has a comparable level of effectiveness to EA, it is associated with higher expenses and greater technical complexity. Our results reinforce the role of EA as the first-line treatment for symptomatic thyroid cysts and PCTNs, given its high effectiveness, low-cost, and good safety profile.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: C.C.Y., Y.H., J.Y.L. Acquisition, analysis, or interpretation of data: C.C.Y., Y.H. Drafting the work or revising: C.C.Y., Y.H., J.Y.L. Final approval of the manuscript: C.C.Y., Y.H., J.Y.L.

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