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EUS-guided Ethanol Ablation of Pancreatic Cysts: An updated Meta-Analysis and Systematic Review

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ABSTRACT

Background: *Pancreatic cyst lesions have increased in incidence due to the widespread use of high-quality imaging worldwide. However, EUS-guided ethanol ablation is emerging in non-surgical candidates as a safe and productive alternative for treating pancreatic cysts. This is an updated meta-analysis and systematic review assessing the safety and outcome of EUS-guided ethanol ablation.*

Methods: *Selection Criteria included pancreatic cyst ablations with EUS-guided ethanol ablation. Data was collected and extracted from Medline, Pubmed, and Ovid journals. Statistical analysis used Fixed and random effects models to calculate the pooled proportions.*

Results: *Upon initial search, 1,420 articles were found, out of which 124 articles were selected and reviewed. Data was extracted from 8 studies (n=188) examining EUS-guided ethanol ablation of pancreatic cysts that met the inclusion criteria. The pooled proportion of patients with complete cyst resolution was 56.08% (95% CI = 48.77 to 63.26). Patients with partial resolution of the pancreatic cyst had a pooled proportion of 16.37% (95% CI = 10.46 to 23.30). The pooled proportion of patients with persistent cysts was 24.72% (95% CI = 17.90 to 32.10). The post-procedural complications included pancreatitis, fever, splenic vein thrombosis, and intractable bleeding that was experienced in some patients. This pooled analysis showed the patients' post-procedural pancreatitis in 5.22% (95% CI = 2.45 to 8.95). Fever and splenic vein thrombosis was noted in 1.63% (95% CI = 0.30 to 40). Intractable bleeding was seen at 2.10 % (95% CI = 0.52 to 4.70). Publication bias calculated using the Harbord-Egger bias indicator was -0.92 (95% CI = -8.61 to 6.77, p = 0.77). The Begg-Mazumdar indicator gave Kendall's tau b value of 0.2 (p = 0.90).*

Conclusions: *EUS-guided ethanol ablation of pancreatic cysts is safe and effective with positive outcomes, especially in non-surgical candidates. This study shows that the intra-procedural and post-procedural complications are low. This modality can be offered as a safe alternative to non-surgical candidates.*

Keyword

Endoscopic ultrasound of pancreas, Ethanol ablation, Pancreatic cysts, Pancreatic cyst ablation, Endoscopic ablation therapy.

Synopsis

EUS-guided ethanol ablation of pancreatic cysts may be a safe alternative to surgical resection in patients with pancreatic cysts. It has been associated with acceptable intra-procedural and post-procedural complications.

Introduction

The increased availability of various imaging modality and their use for diagnostic and screening purposes has increased the diagnosis of pancreatic cysts. These cysts can be categorized into

pseudocysts, cystic neoplasms of the pancreas, and non-neoplastic cysts [1,2]. Most cysts are incidental findings, and patients are asymptomatic, with a 2.5 % incidence in the general population [3]. However, it is essential to differentiate the type of cyst to help with further management. Certain cysts, such as mucinous cystadenomas and intraductal papillary mucinous neoplasms, are at increased risk of progressing to invasive carcinoma [3,4]. Even with high-quality imaging modalities such as CT, MRI, and EUS, there is a morphological overlap. Therefore, EUS-guided fluid aspiration with analysis for tumor markers and pathology has shown increased diagnostic accuracy [5].

The recommended gold standard management option for patients with symptomatic pancreatic cysts, cystic neoplasms, and pre-malignant cysts is surgical resection. However, there is a perioperative morbidity risk of 20-36% and a mortality risk of 2% [6-8]. A safer alternative treatment for patients who are not surgical candidates is EUS-guided pancreatic cyst ablation with ethanol or other chemotherapeutic agents [9,10]. Ethanol is the most commonly used agent for ablation as it is very cost-effective, readily available, and is administered easily. It acts by causing cell membrane lysis, denaturation of the proteins, and occlusion of vessels [11].

Multiple prospective studies, including ethanol ablation, have shown promising outcomes. With ethanol alone, the cyst resolution ranged from 9% to 80 %, and in patients treated with combination therapy, the cyst resolution rate was from 50 % to 80 %. These studies also showed long-lasting effects of the treatment at follow-up visits [12-14]. There are some limitations to these studies, such as small sample sizes, only treatment groups being included, and, in some studies, short follow-up periods. This is an updated meta-analysis and systematic literature review about EUS-guided ethanol ablation of pancreatic cysts. We have evaluated this treatment's clinical outcomes, including cyst response, safety, efficacy, and complications.

Methods

Selection Criteria

EUS-guided ethanol ablation of Pancreatic Cyst studies was selected.

Inclusion Criteria

Studies that used EUS-guided ethanol injections for pancreatic cyst ablation were included.

Exclusion Criteria

Studies with fewer than five patients and studies that did not use ethanol for pancreatic cyst ablation were excluded.

Data Collection

We used Medline (1252), PubMed (1253), Ovid journals (1349), and EMBASE (1351) for the literature review. The numbers we mentioned here are from the initial search reference articles. We searched for articles published from 1966 to 2022 regarding EUS-guided pancreatic cyst ablation therapy. The major gastroenterology journals were searched manually for abstracts regarding the topic. The terms used to search for articles included endoscopic ultrasound of the pancreas, ethanol ablation, pancreatic cysts, pancreatic cyst ablation, and endoscopic ablation therapy. The data searched and extracted was reviewed by both the authors and mutually agreed upon before analysis. Cohen's k was used to quantify the agreement among the reviewers for the data collected.

Quality of Studies

The quality of the clinical trials with control and treatment groups was assessed. We used several criteria to determine the quality of the study (such as randomization, double-blinding, and biases, including selection bias) [15,16]. These criteria did not apply to studies that did not have a control group, as there is no consensus on how to assess these studies [16].

Statistical Analysis

The meta-analysis was conducted by calculating the pooled proportions of the outcomes individually. The first outcome calculated was the pooled proportion of patients with resolution of the pancreatic cyst. The arcsine-based transformation model, such as the Freeman-Turkey variant, was used to transform these pooled data into a quantity. The inverse arcsine variance weights were used for the fixed effects model, and DerSimonian-Laird weights were used for the random effects model. These models were used to calculate the pooled proportion as the back-transform for the weighted mean of the transformed proportions [17,18]. The point estimates about each study's pooled estimate summary were shown using the Forest plots. The width of the point estimates in the forest plots indicated the weight assigned to that study. The effect of publication and selection bias was tested using the Harbord-Egger bias indicator [19] and the Begg-Mazumdar bias indicator [20]. Using the standard error and diagnostic odds ratio, we constructed funnel plots to evaluate potential publication bias [21,22]. Microsoft Excel was used to collect data and for all the analyses.

Results

Our initial literature review found 1,420 articles related to pancreatic cyst ablation. Of those, 124 relevant topics were selected, and a thorough review was performed. We selected eight studies (n=188) that met the inclusion criteria for this study [5,12-14,23-26]. These selected articles were published and available as full-text articles. Figure 1 shows the search data. The pooled estimates were calculated using the fixed effect model.

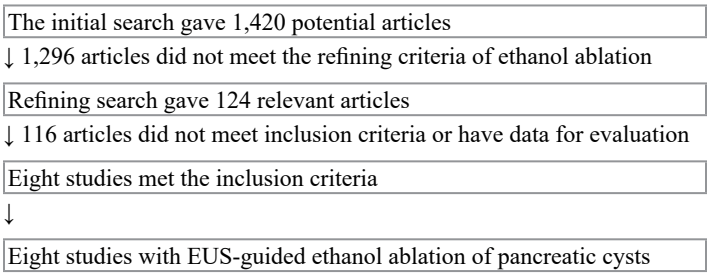

Figure 1: Search results for the meta-analysis.

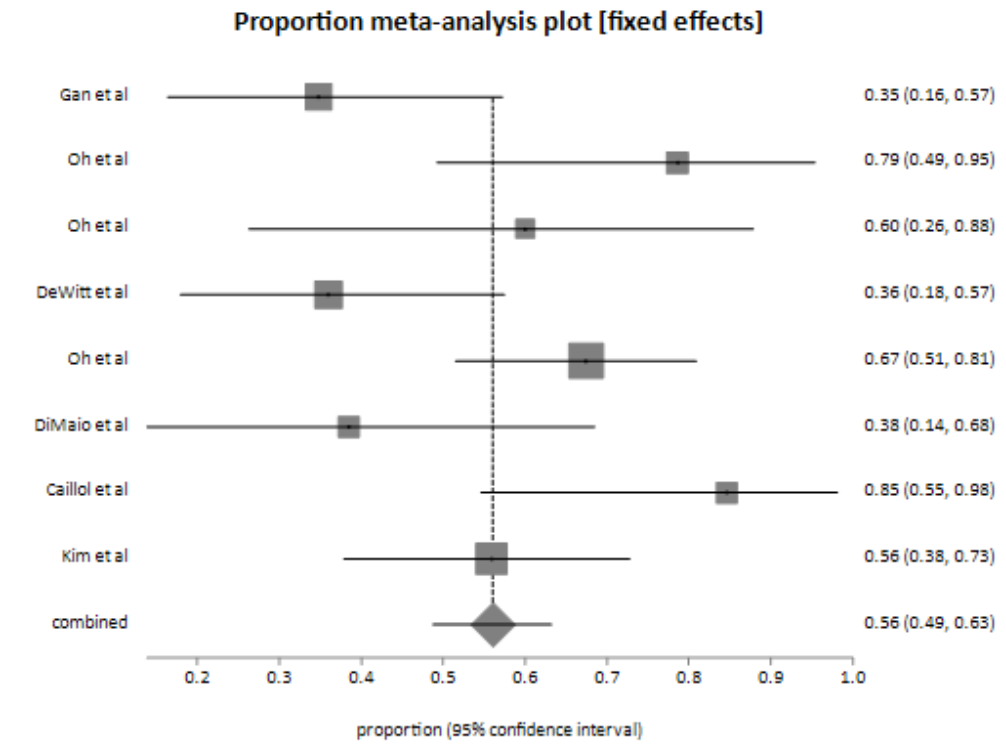

Figure 2: Pooled percentage of patients with complete cyst resolution.

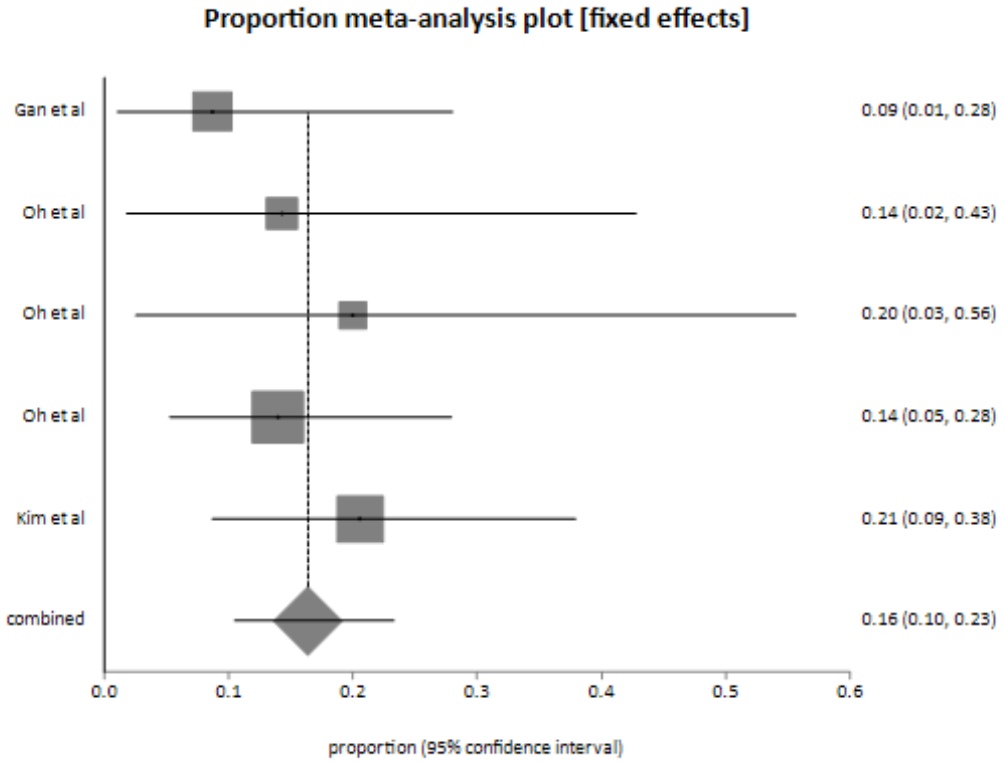

Figure 3: Pooled percentage of patients with partial cyst resolution.

Table 1: Essential Characteristics of the studies included.

Study	Type of Study	Number of patients	Sex M/F	Type of ablation	Complete cyst resolution	Partial cyst resolution	Persistent cyst
Gan et al., 2005	Prospective	25	5/20	Ethanol	8	2	8
Oh et al., 2007	Prospective	14	4/10	Ethanol + Paclitaxel	11	2	1
Oh et al, 2009	Prospective	10	3/7	Ethanol + Paclitaxel	6	2	2
DeWitt et al., 2009	Prospective	25	5/20	Ethanol	9	0	13
Oh et al., 2011	Prospective	52	18/34	Ethanol + Paclitaxel	29	6	12
DiMaio et al., 2011	Retrospective	13	4/9	Ethanol	5	3	5
Caillol et al., 2012	Retrospective	13	7/6	Ethanol	11	0	2
Kim et al., 2017	Prospective	36	12/24	Ethanol + Paclitaxel	19	7	8

This meta-analysis includes 188 patients in total, with 58 males and 130 females. There were 94 patients with unilocular pancreatic cysts and 59 patients with multiple cysts. Among these, 71 patients had pancreatic cysts in the head, 68 in the body, and 50 in the tail of the pancreas. The outcomes were measured by looking at the complete or partial resolution of the pancreatic cysts. This was assessed by repeat CT scans done at the follow-up visits. The pooled proportion of patients with complete cyst resolutions was 56.08% (95% CI = 48.77 to 63.26). Figure 2 shows these pooled proportions. Patients with partial cyst resolutions had a pooled proportion of 16.37% (95% CI = 10.46 to 23.30), as shown in Figure 3. The detailed results of this meta-analysis, including the primary and secondary outcomes, are shown in Table 1.

The pooled intra and post-procedural complications were pancreatitis in 5.22% (95% CI = 2.45 to 8.95), fever and splenic vein thrombosis in 1.63% (95% CI = 0.3 to 4), and intractable bleeding in 2.1% (95% CI = 0.52 to 4.7). The publication bias calculated using the Harbord-Egger bias indicator was -0.92 (95% CI = -8.61 to 6.77, p = 0.77). The Begg-Mazumdar indicator gave Kendall's tau b value of 0.2 (p = 0.90). Figure 4 shows the funnel plots for publication bias. An interobserver variability for data collection among the reviewers gave a Cohen's k value of 1.0.

Discussion

Surgical resection has been the standard of treatment for patients with pancreatic cystic lesions. However, given the high risk of mortality and morbidity associated with surgery, some patients are not ideal surgical candidates. We are looking for more minimally invasive treatment options. Many studies have looked into treating cystic lesions in the liver, spleen, kidney, thyroid, parathyroid, and adrenals by injecting acetic acid, tetracycline, ethanol, or paclitaxel. Ethanol is readily available and has proven to be safe and productive [16,27]. Studies have shown that 80% of ethanol is required to ablate a pancreatic cyst [27] successfully. Ethanol causes tissue necrosis by protein denaturation and dehydration of the epithelial cells, which results in direct coagulation and tissue sclerosis [28-30]. EUS-guided ethanol injection into the pancreatic cyst is more beneficial in many ways. It helps with the targeted delivery of the agent into the cyst with better visualization of the surrounding anatomy than percutaneous injections [29,30]. This meta-analysis looked at the safety and efficacy of EUS-guided ethanol ablation as an alternative treatment option for pancreatic cyst lesions. The primary outcomes we looked at were complete and partial resolution of the pancreatic cysts. This pooled analysis showed a complete resolution of the pancreatic cysts in about 56% of the patients, and partial resolution was noted in 16%.

A 5-80% ethanol injection concentration was used in a study by Gan et al. that showed complete resolution of pancreatic cysts in almost one-third of the patients. This prospective study included 25 poor surgical candidates who underwent cyst ablation with ethanol. All the patients were followed up at 12 months following the ablation, and regardless of the etiology of the cyst, eight patients had complete cyst resolution, eight patients had persistent cysts, and two patients had partial cyst resolution at the end of the study. None of the patients experienced any procedural adverse events [12]. Following this study, Dewitt et al. published a prospective study in 2009 using 80% ethanol for pancreatic cyst ablation. He included 25 patients in this study, and at four months of follow-up, he found that nine patients had complete cyst resolution, 13 patients had persistent cysts, and three patients could not assess the cyst resolution [13]. This evidence was later confirmed again in 2011 and 2012 by retrospective studies done by Dimaio et al. and Caillol et al., respectively. Dimaio et al. used 80 % ethanol in 13 patients, with five patients having complete cyst resolution at 4-month follow-up [23]. Caillol et al. studied the effects of an increased percentage of ethanol in cyst ablations. They used 99 % ethanol for cyst ablations in 13 patients, and at 18 months, follow-ups noted that 11 patients had complete cyst resolution and two patients had persistent cysts [25].

Some studies used a combination of ethanol and paclitaxel. Paclitaxel decreases cell replication by inhibiting the microtubule disassembly during cell division and has been shown to have better outcomes [14]. Oh et al. performed two prospective studies in 2007 and 2009 using ethanol and paclitaxel for pancreatic cyst ablation [4,14]. In 2007, he included 14 patients, and at the 23-month follow-up, he found that 11 patients had complete cyst resolution, 2 had partial cyst resolution, and 1 had a persistent cyst [4]. The follow-up study in 2009 included ten patients, with the majority having septated cysts. These patients were followed up at 18 months; six patients had complete cyst resolution, 2 had partial cyst resolution, and 2 had persistent cysts. Based on this study, combination therapy has better outcomes, especially in patients with complex or septated cysts [14]. These results were later confirmed by another prospective study in 2017 by Kim et al. In this study, both ethanol and paclitaxel combination was used in

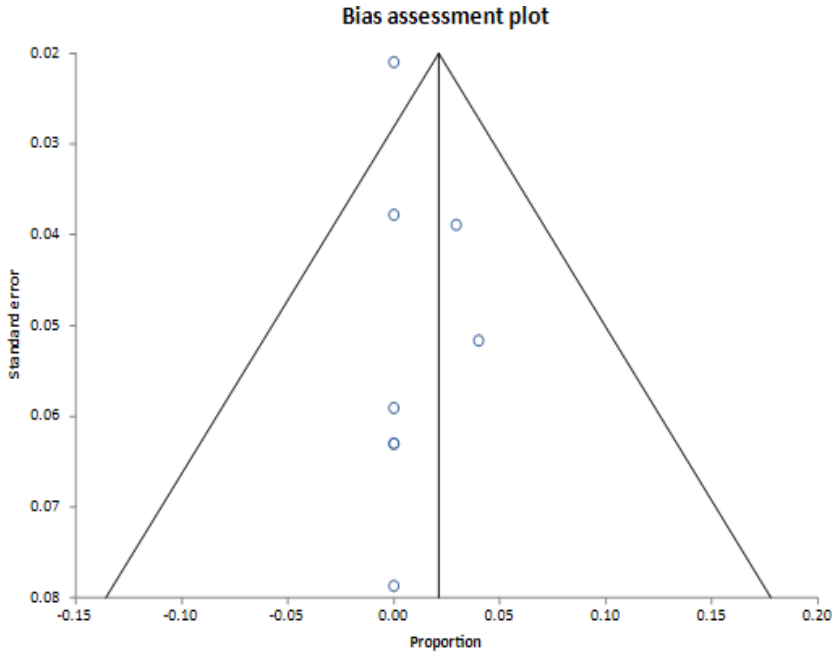

Figure 4: Funnel plot showing publication bias.

36 patients, and at 23 months follow-up, 19 patients had complete cyst resolution, seven patients had partial cyst resolution, and eight patients had persistent cysts [26].

Many factors affect cyst resolution; one of the factors affecting cyst resolution is the type of cysts. Most studies with unilocular cysts had better outcomes compared to septated cysts [5,24]. This meta-analysis found that studies using both combination therapies had better outcomes in septated pancreatic cyst patients [14,26]. Another factor affecting the cyst resolution was the number of times the cyst was ablated. A study by Dimaio et al. showed that the primary outcomes were better in patients who underwent multiple sessions when compared to one session. Of the 13 patients in this study, 0 had complete cyst resolution after one ethanol ablation. On the contrary, five patients were noted to have complete cyst resolution after 2 or 3 ethanol ablation sessions [23]. Despite multiple sessions, procedure-related complications were still low. A study by Dewitt et al. compared ethanol versus saline injections and found that cyst resolution was 80% in the ethanol group compared to 20 % in the saline group. This study also confirmed an additional 33.3 % complete cyst resolution in patients who underwent two sessions of ethanol ablation [13].

The primary complications during and after the procedure included pancreatitis and abdominal pain. This meta-analysis showed the pool of patients with pancreatitis was very low at 5%. Other complications included infection, bleeding, splenic vein thrombosis, and transient hypotension during or after the procedure [11]. These complications are minimal in cystic lesion ablations compared to solid lesions as they form perinodular fibrosis [27,29]. Acute pancreatitis was more prominent when the needle was in close contact with the central pancreatic duct at the time of ethanol injection. Ethanol has cytotoxic effects by zymogen activation, which is thought to cause pancreatitis [23]. Other complications included splenic vein thrombosis, fever, bleeding, and peri cystic spillage. The pooled proportion of patients who underwent resection due to complications was 11. However, there was no regrowth or persistence of the cyst due to the epithelial denudation after ethanol ablation.

This meta-analysis of EUS-guided ethanol ablation of pancreatic cysts has some limitations. There is no direct measure to assess the decrease in malignant potential of the pancreatic cysts after ablation [18]. Expected outcomes are not seen in patients with multiple septations, thicker cysts, or pancreatic cysts with nodules or masses [12]. Some studies included in this analysis did not have a control arm to compare the outcomes. The effect of ethanol ablation at a histologic level was not looked into; only a follow-up CT scan was used to assess the improvement [5,12]. The sample sizes in most studies were small, and the same authors published some studies. Post-procedural follow-up time to determine cyst resolution was relatively shorter in most of the studies. As there were no long-term follow-ups, the benefit of this ablation therapy on mortality and survival was not assessed. There were no studies that compared the outcomes with the standard surgical resection. This meta-analysis and systematic review bias was calculated using Egger and Begg-Mazumdar bias indicators that showed no statistically significant bias. Furthermore, funnel plots were used to represent publication bias among the studies included in the present analysis, as shown in Figure 4.

Conclusions

EUS-guided ethanol ablation of pancreatic cysts is safe and effective with positive outcomes, especially in non-surgical candidates. This study shows that the intra-procedural and post-procedural complications are low. This modality can be offered as a safe alternative to non-surgical candidates.

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