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Are Non-Ethanol Based Ablation Therapies Better Than Ethanol Ablation for Pancreatic Cysts?: A Systematic Review and Meta-Analysis.

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ABSTRACT

Background: *Endoscopic Ultrasound (EUS) guided Ethanol Ablation of the pancreatic cyst has been used as an alternative for surgery in recent years. In this meta-analysis, we compare the outcomes of pancreatic cyst ablation with ethanol-based ablation therapy versus non-ethanol-based ablation therapies.*

Methods: *Selection Criteria included pancreatic cyst ablations with EUS-guided ethanol and non-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, 1,510 articles were found, out of which 131 articles were selected and reviewed. Data was extracted from nineteen studies (n=609) which looked at EUS-guided ablation of pancreatic cysts that met the inclusion criteria. Of the nineteen studies, eight (n=390) used EUS-guided ethanol ablation. Four (n=88) studies used ethanol with a paclitaxel combination for ablation, and seven (n=131) used non-ethanol-based ablations alone. The non-ethanol-based ablations included Paclitaxel, Paclitaxel, Gemcitabine combination, or Lauromacrogol. The pooled proportion of patients with complete cyst resolution in the ethanol group was 61.11% (95% CI = 56.25 to 65.86), ethanol with paclitaxel group was 54.34% (95% CI = 44.03 to 64.46), and the non-ethanol group was 49.59 % (95% CI = 41.19 to 58.01). Patients with partial cyst resolution had a pooled proportion of 7.41% (95% CI = 5.03 to 10.2) in the ethanol group, 27.45% (95% CI = 18.77 to 37.08) in the ethanol with paclitaxel group, and 29.16% (95% CI = 21.82 to 37.11) in the non-ethanol group. The pooled proportion of patients with persistent cysts was 45.57% (95% CI = 43.87 to 47.28) in the ethanol group, 6.93% (95% CI = 2.63 to 13.05) in the ethanol with paclitaxel group, and 21.17% (95% CI = 14.71 to 28.45) in the non-ethanol group. Procedure-related complications, including pancreatitis, were noted in a pooled proportion of 8.08% (95% CI = 5.51 to 11.11) in the ethanol group, which was relatively higher compared to 5.82% (95% CI = 1.95 to 11.56) in the ethanol with paclitaxel group, and 3.91% (95% CI = 1.31 to 7.83) in the non-ethanol group. Other complications included post-procedure infec-*

tion with a pooled proportion of 1.13% (95% CI = 0.3 to 2.47) in the ethanol group, 2.84% (95% CI = 0.43 to 7.26) in the ethanol with paclitaxel group, and 1.87% (95% CI = 0.27 to 4.83) in the non-ethanol group. The pooled proportion of patients who had procedure-related abdominal pain was 19.06% (95% CI = 15.18 to 23.25) in the ethanol group, which was significantly higher when compared to ethanol with paclitaxel group which was 9.58% (95% CI = 4.4 to 16.48), and 9.11% (95% CI = 4.85 to 14.53) in the non-ethanol group. Publication bias calculated using the Harbord-Egger bias indicator gave a value of 2.3 (p = 0.09). The Begg-Mazumdar indicator gave Kendall's tau b value of 0.28 (p = 0.39).

Conclusions: *EUS-guided pancreatic cyst ablation is an alternative therapy for non-surgical candidates. This study showed that complete cyst resolution was comparable in patients with ethanol and non-ethanol ablation. Procedural adverse events were minimal in all the treatment groups, suggesting that pancreatic cyst ablation is safe.*

Keywords: Endoscopic ultrasound of pancreas, ethanol ablation, pancreatic cysts, pancreatic cyst ablation, paclitaxel ablation, and endoscopic ablation therapy.

Introduction:

Pancreatic cyst diagnosis has increased in recent years with the wide availability of cross-sectional imaging modalities (4). Incidentally, pancreatic cysts are treated conservatively, and in recent years, pancreatic cyst ablation using EUS-guided therapies has become more popular (1,22). Pancreatic cysts have heterogeneous lesions, including pseudocysts, retention cysts, and cystic neoplasms (3). Most of these are incidentally asymptomatic in presentation and can present with pancreatitis due to cyst compression on the surrounding tissue (16). Pancreatic cyst progression to malignancy varies depending on the type of cyst. Mucinous cystic neoplasms (MCN) and intraductal papillary neoplasms (IPMN) are particularly at risk of progressing to malignancy (17). The standard treatment for these lesions includes surgical resection. However, there is a 10-20% morbidity and 1-3% rate of mortality associated with resection (16,18). Imaging techniques alone do not help with the appropriate diagnosis of these lesions and need tissue sampling to confirm. EUS-guided FNA is rapidly becoming essential in evaluating these lesions for cyst-fluid cytology and tumor-marker analysis (3). During the EUS aspiration procedure, lavage of the pancreatic-cyst cavity with an ablative agent such as ethanol can be done in one sitting (19). Ethanol, in particular, has been used in many studies for pancreatic cyst ablations, as it is inexpensive, readily available, and has the potential to rapidly ablate the entire cyst wall. The mechanism of action of ethanol is through cell membrane lysis and protein degeneration (9).

Conversely, Paclitaxel causes apoptosis by inhibiting the microtubule-dependent processes, which induce cessation of cellular division. Some studies have shown longer-lasting effects in patients who received a combination ablation with ethanol and chemotherapeutic agents (20,21). Paclitaxel is a very hydrophobic and viscous chemotherapeutic agent and can exert long-term effects within a closed cystic cavity with low leakage through the puncture site (10,17).

Multiple studies have shown that EUS-guided ablation is feasible and safe in patients who are not sur-

gical candidates. Multiple studies looked at EUS-guided ethanol ablation with varying rates of complete cyst resolutions (2,3,11). These studies showed that this technique is safe and has minimal procedural adverse events, with the treatment effects well maintained on long-term follow-ups and quality of life (11,23). Procedural adverse events include post-ablation pancreatitis, which is suspected to be a direct cytotoxic effect of the ethanol in the ductal epithelium. Unintentional injection of the ablative agent into the pancreatic parenchyma or inflammatory effects of alcohol on the surrounding tissues by pericystic leakage resulting in pancreatitis (5,6,24). Recent studies are looking at ethanol-free regimens with similar complete cyst resolution rates and superior safety compared to ethanol-containing regimens (16).

Methods:

Selection criteria: EUS-guided ablation of Pancreatic Cysts with either ethanol or other chemotherapeutic agent studies were selected.

Inclusion criteria: Studies using EUS-guided pancreatic cyst ablation ablation were included.

Exclusion criteria: Studies with fewer than five patients and studies that did not use EUS-guided ablation of pancreatic cyst ablation were excluded.

Data collection: We used Medline (452), PubMed (528), Ovid journals (630), and EMBASE (531) for the literature review. The numbers we mentioned here are from the initial search reference articles. We searched for articles published from inception 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.

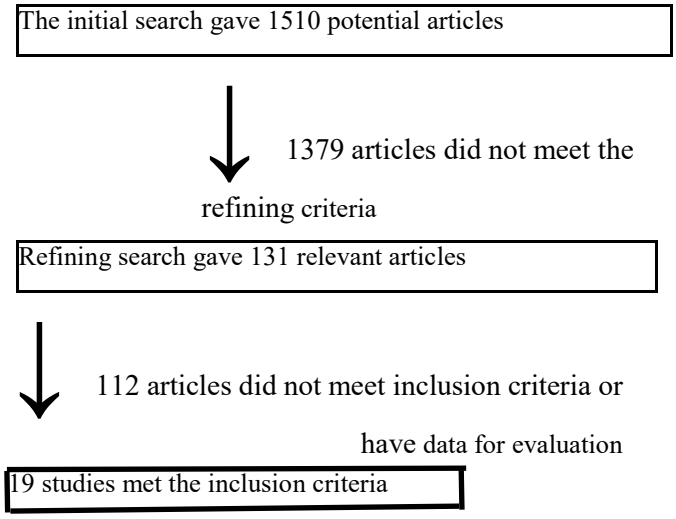
Quality of studies: The quality of the clinical trials with control and treatment groups was assessed. We used several criteria to determine the quality of the study (such as randomization, double blinding, and biases, including selection bias) (25,27). These criteria did not apply to studies that did not have a control group, as there is no consensus on how to assess these studies (25).

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 a weighted mean of the transformed proportions (26). The point estimates with the pooled estimate summary in each study are 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 and Begg-Mazumdar bias indicators (28). Using the standard error and diagnostic odds ratio (25), we constructed funnel plots to evaluate potential publication bias.

Microsoft Excel was used to collect data and for all the analyses.

Results: Our initial literature review found 1510 articles related to pancreatic cyst ablation. Of those, 131 relevant articles were selected, and a thorough review was performed. We selected 19 studies (n=609) that met the inclusion criteria for this study. 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. We included 8 (n=390) studies that used EUS-guided ethanol ablation, 4 (n=88) studies that used ethanol with paclitaxel ablation, and 7 (n=131) studies that used nonethanol-based ablations. The non-ethanol-based ablations included Paclitaxel, Paclitaxel with Gemcitabine combination, or Lauromacrogol.

Figure 1:
Search data for the meta-analysis



In this meta-analysis, 609 patients were included, with 200 males and 377 females. Among these, 241 patients had pancreatic cysts in the head, 186 in the body, and 118 in the tail of the pancreas. The primary outcome measured was complete cyst resolution with ethanol or non-ethanol-based guided pancreatic cyst ablation therapies. The secondary outcomes included partial cyst resolutions and persistent cysts with individual treatment groups. This was assessed by repeat CT scans done at the follow-up visits. The pooled proportion of patients who had complete cyst resolution in the ethanol group was 61.11% (95% CI = 56.25 to 65.86), ethanol with paclitaxel group was 54.34% (95% CI = 44.03 to 64.46), and the non-ethanol group was 49.59 % (95% CI = 41.19 to 58.01). Figure 2 shows these pooled proportions. Partial cyst resolution was the secondary outcome that was measured with a pooled proportion of 7.41% (95% CI = 5.03 to 10.2) in the ethanol group, 27.45% (95% CI = 18.77 to 37.08) in the ethanol with paclitaxel group, and 29.16% (95% CI = 21.82 to 37.11) in the non-ethanol group. This pooled analysis is shown in Figure 3. The pooled proportion of patients with persistent cysts was 45.57% (95% CI = 43.87 to 47.28) in the ethanol group, 6.93% (95% CI = 2.63 to 13.05) in the ethanol with paclitaxel group, and 21.17% (95% CI = 14.71 to 28.45) in the non-ethanol group. Procedure-related pancreatitis was the major complication, with a pooled proportion of 8.08% (95% CI = 5.51 to 11.11) in the ethanol group. This was higher than 5.82% (95% CI = 1.95 to 11.56) in the ethanol with paclitaxel group and 3.91% (95% CI = 1.31 to 7.83) in the non-ethanol group. Other complications included post-procedure infection with a pooled proportion of 1.13% (95% CI = 0.3 to 2.47) in the ethanol group, 2.84% (95% CI = 0.43 to 7.26) in the ethanol with paclitaxel group, and 1.87% (95% CI = 0.27 to 4.83) in the non-ethanol group. The pooled proportion of patients who experienced post-procedure abdominal pain was also significantly higher in the ethanol group, measuring about 19.06% (95% CI = 15.18 to 23.25) when compared to ethanol with paclitaxel group, which was 9.58%

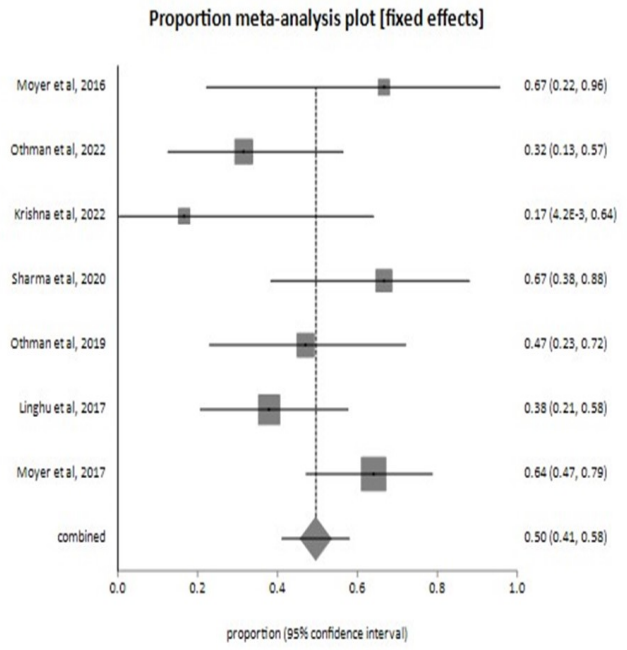
(95% CI = 4.4 to 16.48), and 9.11% (95% CI = 4.85 to 14.53) in the non-ethanol group. The publication bias calculated using the Harbord-Egger bias indicator was 2.3 (p = 0.09). The Begg-Mazumdar indicator gave Kendall's tau b value of 0.28 (p = 0.39). Figure 4 shows the funnel plots for publication bias. An interobserver variability for data collection among the reviewers gave a Cohen's k value of 3.0.

Figure 2:

Eight studies used ethanol alone, four studies used a combination of ethanol and paclitaxel, and seven studies used non-ethanol therapies.

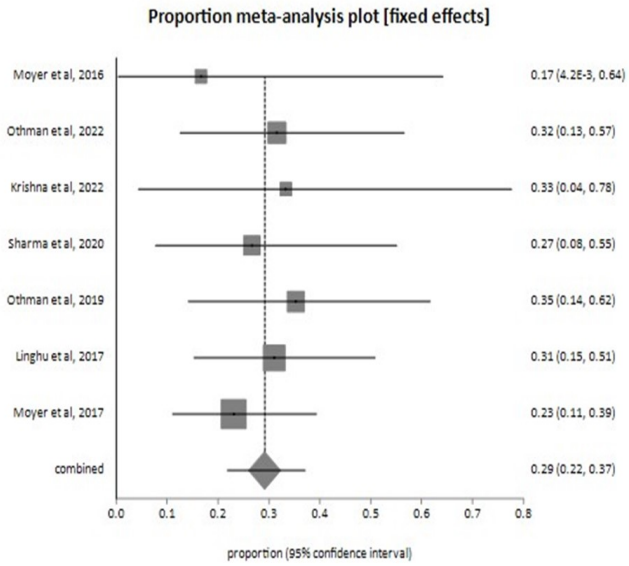
Pooled Proportion of complete Cyst resolution with Non Ethanol based Ablation.

Figure 3:



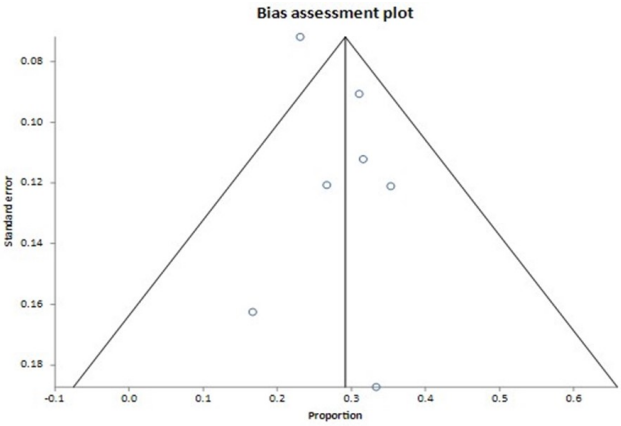
Pooled Proportion of Partial Cyst resolution with Non Ethanol based Ablation

Figure 4:



Funnel Plot showing Publication Bias

Figure 5:



Discussion:

The incidence of pancreatic cystic neoplasms is increasing, with an overall prevalence of 2% worldwide (12,13). Many pancreatic cysts have minimal malignant potential, but the majority of the mucinous cysts, like Mucinous Cystic Neoplasms (MCNs) and Intraductal Papillary Mucinous Neoplasms (IPMNs), have a higher potential to progress to pancreatic cancer. The natural history of this is unclear, but the overall risk of progression to malignancy is approximately 25%. This risk is linked to several high-risk features of the pancreat-

ic lesions (14). EUS-guided ablation of these pancreatic cystic lesions could prevent the advancement of pancreatic cancer in a select group of patients. Multiple studies so far have shown that the use of ethanol for pancreatic cyst ablation is safe and effective, with the efficacy rate ranging from 60 to 79%, and newer trials have shown that the use of combination treatment with paclitaxel has long-term durability of the cyst ablation. Some studies have shown that this combination therapy in patients who undergo sufficiency ablation will eliminate baseline KRAS mutations (7,8). Most of the studies to date have experienced some adverse events and are thought to be from the extravasation of ethanol into the surrounding pancreatic parenchyma (14,15). Therefore, we performed this meta-analysis to examine the efficacy and safety of ethanol and non-ethanol-based ablation treatments for pancreatic cysts.

This is the first meta-analysis comparing the outcomes of EUS-guided pancreatic cystic lesions with ethanol, ethanol with paclitaxel, and non-ethanol-based treatments. Previous meta-analysis by Reddy et al. in 2024 looked at the cyst resolution and safety with ethanol ablation only (29). A poster presented by Salih et al. assesed the outcomes with different ablation techniques but this was also not a comparative study (30). Another meta-analysis published by Saghir et al. in 2021 compared the outcomes of ethanol ablation and ethanol with paclitaxel; however, no studies so far looked at included non-ethanol-based therapies (20). Our meta-analysis found that patients who underwent ethanol alone pancreatic cyst ablations had 61 % complete cyst resolution. This falls in the previously known range done in prior meta-analyses comparing the outcomes. Gan et al. 2005 first published a prospective study including 25 patients who used ethanol alone for ablation and had eight patients with complete cyst resolution (3). This has been improved in newer studies, as seen in the most extensive retrospective study published by Choi et al. in 2019, which included 214 patients with complete cyst resolution noted in 147 patients. This was thought to be with higher concentrations of ethanol, and multiple sessions of cyst ablations were done to improve the outcomes (2).

These results are compared with ablation therapies using ethanol and paclitaxel with a complete cyst resolution rate of 54 %. Patients in the non-ethanol-based therapy group had a 50 % complete cyst resolution. Moyer et al. 2016 (CHARM trial) published a comparative prospective study including ten patients, of which four underwent ablation with combination therapy including ethanol and paclitaxel, and six patients underwent ablation with paclitaxel alone. Three patients in the combination group had complete cyst resolution at the 12-month follow-up, and one had a persistent cyst. A total of 4 patients in the paclitaxel group had complete cyst resolution, and one patient had partial cyst resolution. There was only one patient who had a persistent cyst. Complete ablation was achieved in 67 % of patients in the non-ethanol group at both 6 and 12 months. In contrast, in that study, the ethanol group recorded complete ablation rates of 50 % and 75 % at 6 and 12 months, respectively (12). This suggests that non-ethanol-based therapies have better outcomes at short and long-term follow-ups.

This meta-analysis also looked at partial cyst resolution at follow-up visits. We found that the partial cyst resolution was up to 7% in the ethanol group compared to 27 % in the combination therapy group. However, around 30% partial resolution was

noted in the non-ethanol-based therapy. These patients mostly had multiple cysts and solid components. This shows that non-alcohol-based therapies help break down the solid component and are also better in oligocystic lesions. The most recent prospective study published in 2022 by Othman et al.

included 19 patients. Of the 19 patients, 17 were diagnosed with complex IMPN with multiloculations. They underwent only paclitaxel ablation, and at 6-month follow-up, six patients were noted to have complete cyst resolution. Six patients had partial cyst resolution, and five were reported to have persistent cysts (13). Therefore, studies with multiple chemotherapeutic agent ablations alone must be examined with more extended follow-up visits.

Procedure-related adverse events included post-procedure pancreatitis, which was higher in the ethanol group by up to 8%. This was compared to the combination group, which had only 5%, and the non-ethanol group had only 3% of the patients with pancreatitis. This suggests that the use of ethanol does increase the risk of pancreatitis. Another major complication requiring hospitalization was abdominal pain, which was also higher in the ethanol-alone group up to 20 %. This adverse event was documented in 10 % of the combination group and 9 % in the ethanol-free group. Infection was noted in 1-2 % in all three groups. Choi et al. in 2019 included 214 patients with pancreatic cysts who underwent ethanol-alone ablation. Out of the 214 patients, they noted 21 patients experienced pancreatitis, and 47 patients overall were hospitalized for abdominal pain (2). However, compared to surgery-related mortality and morbidity, EUS-guided therapies have a lesser overall complication rate of < 20 %. Some limitations of this study include a smaller study population in the non-ethanol group compared to the ethanol ablation group. The doses of the ablative agents were not standardized, as there are no available guidelines. Shorter follow-up periods were the other limitation, as most non-ethanol studies had an average of 6-month follow-ups as these are newer studies. Not all studies included CEA levels, the cysts' premalignant state, or the malignant progression after ablation. Only one study used a combination of paclitaxel and gemcitabine, and we need more studies using a combination of chemotherapy drugs with more extended follow-up periods.

Conclusions:

EUS-guided pancreatic cyst ablation is an alternative therapy for non-surgical candidates. This study showed that complete cyst resolution was comparable in patients with ethanol and non-ethanol ablation. Procedural adverse events were minimal in all the treatment groups, suggesting that pancreatic cyst ablation is safe.

Synopsis:

EUS-guided ablation of pancreatic cysts is a safe alternative to surgical resection in patients with pancreatic cysts. We are comparing the outcomes with ethanol-based ablation and non-ethanol-based ablations.

Conflict of Interest and Financial Disclosure:

Yeshaswini Reddy, Tulika Chatterjee, and Srinivas R Puli declare that they have no conflict of interest, grant, or financial disclosure. This study did not recieve any funding in any form.

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