Safety and efficacy of EUS-guided ablation of pancreatic lesions with ethanol versus ethanol with paclitaxel: A systematic review and meta-analysis

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ABSTRACT

Background and Objectives: EUS-guided ethanol ablation has emerged as an alternative method for pancreatic lesions. Recently, paclitaxel was added to ethanol to assess ablative effects in pancreatic lesions. We performed a systematic review and meta-analysis on EUS-guided ethanol ablation (EUS E) versus EUS-guided ethanol with paclitaxel (EUS EP) ablation for the management of pancreatic lesions.

Methods: Comprehensive search of multiple electronic databases and conference proceedings including PubMed, EMBASE, Google Scholar, and Web of Science databases (from inception to May 2020). The primary outcome evaluated complete ablation of the lesions radiologically and the secondary outcome evaluated adverse events (AEs).

Results: Fifteen studies on 524 patients were included in our analysis. The pooled complete ablation rate was 58.89% (95% confidence interval (CI) = 38.72–77.80, F = 91.76%) and 55.99% (95% CI = 44.66–67.05, F = 0) in the EUS E and EUS EP groups (P = 0.796), respectively. The pooled AE rates were 13.92% (95% CI = 4.71–26.01, F = 83.43%) and 31.62% (95% CI = 3.36–68.95, F = 87.9%) in the EUS E and EUS EP groups (P = 0.299), respectively. The most common AE was abdominal pain at 7.27% (95% CI = 1.97–14.6, F = 68.2%) and 12.44% (95% CI = 0.00–39.24, F = 81.1%) in the EUS E and EUS EP groups (P = 0.583), respectively. Correlation coefficient (r) was –0.719 (P = 0.008) between complete ablation and lesion size. Conclusion: Complete ablation rates were comparable among both groups. AE rates were higher in the EUS EP group. Further randomized controlled trials are needed to validate our findings.

Key words: ethanol, lesions, meta-analysis, paclitaxel, pancreatic

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INTRODUCTION

Pancreatic lesions present as a wide clinicopathologic spectrum of lesions.[1] The many types of pancreatic lesions include, but are not limited to, serous mucinous neoplasms (SCN), mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasms (IPMN), solid pseudopapillary neoplasms, pancreatic neuroendocrine tumors (PNET), and pancreatic fluid collections (PFC) including pseudocysts and walled off pancreatic necrosis (WON).[2] Of primary concern is the risk of malignant transformation of pancreatic lesions. The risk of malignancy in a pancreatic cyst at the time of diagnosis is at most 0.01% or 0.21% for cysts >2 cm.[3] EUS-FNA is an important tool in the evaluation of these lesions by means of cyst-fluid cytology and tumor-marker analysis.[4]

In most individuals depending on the indication, surgery or surveillance may be an appropriate management for pancreatic lesions.[5] However, surgical resection of pancreatic lesions carries significant perioperative morbidity (20%–40%) and mortality (rates as high as 2%), so there is considerable interest in minimally invasive interventions that could serve as alternatives to surgery.[5,6,8] This is especially helpful in those who may be high risk for surgery or reluctant to undergo pancreatic surgery.[9]

EUS-guided ablation with ethanol or ethanol plus paclitaxel is a minimally invasive method for the management of pancreatic lesions.[8,16,11] This procedure was first described by Gan et al. in 2005. Cystic lesions in solid organs have been successfully ablated by utilizing chemical injection, with the most common injectates being ethanol and paclitaxel.[12] Ethanol induces lysis of the cell membrane and protein denaturation, with ablative effects on the cyst epithelium.[13] Paclitaxel exerts its effect on cystic lesions by inhibiting microtubule-dependent processes which induces cessation of cellular division followed by apoptosis.[8] The effects are long lasting.[8]

Studies utilizing ethanol[1,14-16] for pancreatic lesion ablation have had varying results regarding resolution (9%–80%), whereas ethanol plus paclitaxel[11,17-19] showed improved resolution (50%–79%) with long-lasting effects.[20] However, the data on long-term outcomes are limited. Currently, this intervention has been utilized as an investigative modality on patients who refused surgery or were poor surgical candidates.[9]

We performed a systematic review and meta-analysis comparing the safety and efficacy of EUS-guided ethanol ablation versus EUS-guided ethanol plus paclitaxel ablation of pancreatic lesions.

METHODS

Search strategy

We performed a comprehensive search through several databases such as PubMed, EMBASE, Web of Science, and Google scholar (from inception to May 2020). A combination of keywords used in our literature search were as follows: “EUS,” “endoscopic,” “ultrasound.” “pancreatic,” “cyst,” “ablation,” “ethanol,” and “paclitaxel.” A manual search of the references section of the selected articles was also performed to find additional relevant articles. Two authors (BD and SS) carried out the search and reviewed the articles individually. A third author (YN) reviewed studies which had discrepancies for resolution. Articles that did not meet the inclusion criteria were excluded. We utilized the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines during our search for studies utilizing EUS-guided ethanol ablation versus ethanol plus paclitaxel ablation of pancreatic lesions.[21] Refer to Supplementary Figure 1.

Study selection

Studies evaluating the clinical efficacy and adverse events (AEs) of EUS-guided ethanol ablation and ethanol with paclitaxel ablation for pancreatic lesions were reviewed. We included studies in our analysis, which reported the use of ethanol or ethanol plus paclitaxel for the management of pancreatic lesions as long as they had data to be extracted and did not fulfill criteria for exclusion. All of our patients were over 18 years and were included regardless of the number of lesions or loculations. We also included studies reporting outcomes on any type of pancreatic lesion irrespective of whether it was suspected to be benign, indeterminate, or malignant and regardless of symptoms. The following exclusion criteria were used (1) studies utilizing other methods to ablate a pancreatic cyst, (2) ages <18 years old or prisoners, (3) studies not in the English language, and (4) studies with <10 patients. In the event of cohort overlap, the most appropriate study was selected, and the other was excluded.
Data abstraction and quality assessment

Quality assessment of the studies was performed independently by two authors (BD and SS). Any differences were discussed with a third author (YN) to reach a consensus between the authors. The Newcastle–Ottawa scale was used to assess the quality of the cohort studies. Quality assessment for randomized controlled trials was done with the Jadad–Oxford scale.

Outcomes assessed

The primary outcome was the complete ablation success rate of pancreatic lesions with either ethanol or ethanol plus paclitaxel.

The secondary outcomes of the study included overall AE and adverse event subtypes.

Definitions

In most studies, response to treatment was assessed by comparing the original lesion volume to post treatment lesion volume by either EUS, computed tomography or magnetic resonance imaging. The response was interpreted as complete resolution, which was defined as either no visualization of the lesion or at least ≥95% reduction of lesion volume on follow-up imaging.

Statistical analysis

We utilized the meta-analysis technique suggested by DerSimonian and Laird to calculate the pooled estimates for each outcome of interest by following the random effects model. If a value of zero occurred in the outcome of a study, then a value of 0.5 was added before statistical analysis. The Cochran Q statistical test and I² statistics were utilized to assess heterogeneity. Heterogeneity was classified by the values of <30%, 30%–60%, 61%–75%, and >75%, which suggest low, moderate, substantial, and considerable heterogeneity, respectively. We utilized the Pearson correlation coefficient (r) to investigate potential association of pancreatic lesion size with complete ablation. All analyses were performed using STATA v16.1 software (StataCorp, LLC College Station, TX).

RESULTS

Search results and population characteristics

Fifteen studies from an initial pool of 598 studies reporting data on EUS-guided ethanol (EUS E) ablation and EUS-guided E + P ablation (EUS EP) were included in our final analysis. The final meta-analysis included 14 cohort studies and 1 randomized controlled trial. Twelve studies were prospective and three were retrospective. Thirteen studies were single center and two were multi-center. No studies were population based. The quality assessment of the studies can be viewed in Supplementary Table 1.

The EUS E group included 142 males (35%) and 265 females (65%). The EUS EP group included 30 males (36%) and 54 females (64%). The mean age in years was 59.3 and 57 in the EUS E and EUS EP groups, respectively. The location of the lesion was reported in 10 of the 11 studies in the EUS E group and 3 of the 4 studies in the EUS EP group. The most common lesion location in the EUS E group was the head/uncinate process (43%) followed by the body (32%), then the tail (25%) of the pancreas. The most common lesion location in the EUS EP group was the tail (52%) followed by the head/uncinate process (34%), then body (13%) of the pancreas. The mean follow-up period in months for the EUS E versus EUS EP groups was 28.3 and 18.2, respectively. Table 1 outlines the characteristics of the included studies.

Meta-analysis outcomes

Primary outcome

The pooled complete ablation rate was 58.89% (95% CI = 38.72–77.80, I² = 91.76%) and 55.99% (95% CI = 44.66–67.05, I² = 0) in the EUS E and EUS EP groups (P = 0.796), respectively. Figure 1 displays the forest plots for the complete ablation rates for ethanol and ethanol with paclitaxel.
forest plots for the complete ablation rates for EUS E and EUS EP.

Secondary outcomes

The pooled overall adverse event (AE) rates were 13.92% (95% confidence interval (CI) = 4.71–26.01, \(I^2 = 83.43\%\)) and 31.62% (95% CI = 3.36–68.95, \(I^2 = 87.9\%\)) in the EUS E and EUS EP groups (\(P = 0.299\)), respectively. The most common AE was abdominal pain at 7.27% (95% CI = 1.97–14.6, \(I^2 = 68.2\%\)) and 12.44% (95% CI = 0.00–39.24, \(I^2 = 81.1\%\)) in the EUS E and EUS EP groups (\(P = 0.583\)), respectively. Postprocedure pancreatitis was the next most common AE at 3.14% (95% CI = 0.60–6.91, \(I^2 = 33.01\%\)) and 3.78% (95% CI = 0.00–15.32, \(I^2 = 47.84\%\)) in the EUS E and EUS EP groups (\(P = 0.769\)), respectively. The correlation coefficient (\(r\)) was -0.719 (\(P = 0.008\)) between complete ablation and pancreatic lesion size. AEs are detailed in Table 2.

Validation of meta-analysis results

Sensitivity analysis

One study at a time was excluded to evaluate its effect on the main outcome and we found that no single study had a significant effect on the main outcome or the heterogeneity.

Heterogeneity

Utilizing the Q statistics and \(I^2\) analysis for heterogeneity, considerable heterogeneity was noted in the EUS E group and low heterogeneity was noted in the EUS EP group for the primary outcome.

Considerable heterogeneity was noted in the overall AE for both groups. Considerable heterogeneity was noted in the EUS EP group and substantial heterogeneity in the EUS E group for abdominal pain. Moderate heterogeneity was noted in postprocedural pancreatitis for both groups.

Publication bias

It was difficult to estimate publication bias since we are evaluating small, one arm studies with dichotomous outcomes.

DISCUSSION

To our knowledge, this is the first meta-analysis comparing the outcomes of EUS E versus EUS EP ablation for pancreatic lesions. Our study demonstrated that, in patients with pancreatic lesions undergoing EUS E ablation or EUS EP ablation, the rates of complete ablation were comparable.

Based on our analysis, the pooled complete ablation rates were comparable between the EUS E and EUS EP groups at 58.89% versus 55.99%, respectively. Complete ablation rates in the EUS E and EUS EP groups ranged from 8.7% to 100% and 45%–75%, respectively. In the EUS E group, studies which conducted treatments on PNET had greater complete ablation rates as compared to those involving other types of pancreatic lesions (MCN, SCN, IPMN, PFC, and WON). However, there were no PNETs
treated in the EUS EP group and the complete ablation success rate was not limited to any specific types of lesions. Furthermore, it was reported that unilocularity was a contributing factor to complete ablation rates as injection of a therapeutic agent into the cyst could reach the entire lining, without being blocked by septations, but several studies from our meta-analysis had varying results regarding this.\[8,10,15,16,29\]

The pooled AE rates were greater in the EUS EP group as compared to the EUS E group at 31.62\% versus 13.92\%, respectively. This finding was not statistically significant (P = 0.299) and is likely underpowered due to the smaller number of patients in the EUS EP group as compared to the EUS E group (88 vs. 436), respectively. Abdominal pain was the most common AE followed by postprocedural pancreatitis in the EUS E and EUS EP groups with comparable rates at 7.27\% vs 12.44\% and 3.14\% versus 3.78\%, respectively. One study from the EUS E group had the most cases of post procedural pancreatitis (21) and the risk for pancreatitis was attributed to having multilocular cysts, sticky cystic fluid, or ethanol leakage from the pancreatic lesion. In the study by Park et al., pancreatitis risk increased when more than 2 ml of ethanol was utilized for lavage.\[34\]

There was a strong negative correlation between complete ablation rates and pancreatic lesion size with an r value of ~0.719 (P = 0.008). This makes intuitive sense and suggests that complete ablation is more likely when pancreatic lesions are small. One study in the EUS EP group reported a cyst size <35 mm to be predictive of complete ablation and 2 studies in the EUS E group reported cyst sizes <27 mm to be predictive of complete ablation.\[10,15,34\]

This study has several limitations. The study population was small in the EUS EP group. There was substantial to considerable heterogeneity. There is a paucity of randomized controlled trials. Varying doses of the ablative agents were utilized, since there are no current guidelines to follow. There were not enough resected specimens to study the effects of what ablative agents do to pancreatic lesions. The average follow-up period was lower in the EUS EP group at 18.2 months as compared to 28.3 months in the EUS E group. Longer follow up periods should be pursued in future studies to assess long-term effects of chemical ablation despite resolution of cysts on initial follow-up. Furthermore, the longer follow-up will allow for assessment of mucinous cysts as degeneration may take up to 5–10 years.\[10,15,39\]

In summary, this study showed comparable rates of complete ablation between the EUS E and EUS EP groups. There was a strong negative correlation between complete ablation rates and smaller lesion sizes. The overall AE rates were found to be greater in the EUS EP group, but the rates of abdominal pain and postprocedural pancreatitis were comparable between both groups. Future studies should evaluate paclitaxel’s effect alone on pancreatic lesions to assess

| Author | Total number of AE | Pancreatitis | Bleeding | Perforation | Infection | Abdominal pain | Others |
|--------|---------------------|--------------|----------|------------|-----------|----------------|--------|
| Caillol et al.\[15\] | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Choi et al.\[29\] | 71 | 21 | 1 | 0 | 1 | 47 | 1 |
| Gan et al.\[12\] | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gómez et al.\[16\] | 2 | 1 | 0 | 0 | 0 | 1 | 0 |
| Levy et al.\[30\] | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Matsumoto et al.\[34\] | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Paik et al.\[33\] | 4 | 1 | 0 | 0 | 0 | 2 | 1 |
| Song et al.\[34\] | 11 | 2 | 0 | 0 | 0 | 6 | 1 |
| Qin et al.\[34\] | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Park et al.\[34\] | 29 | 3 | 0 | 0 | 0 | 18 | 8 |
| Park et al.\[34\] | 5 | 3 | 0 | 0 | 0 | 1 | 1 |
| Ethanol and paclitaxel | | | | | | |
| Oh et al.\[35\] | 3 | 1 | 0 | 0 | 0 | 1 | 1 |
| Oh et al.\[37\] | 7 | 0 | 1 | 0 | 0 | 5 | 1 |
| DeWitt et al.\[11\] | 9 | 3 | 0 | 0 | 1 | 4 | 1 |
| Moyer et al.\[39\] | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

AE: Adverse event
any advantage from a safety and efficacy standpoint. Further randomized control trials are needed to validate our findings.

**Supplementary Materials**

Supplementary information is linked to the online version of the paper on the *Endoscopic Ultrasound* website.

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Nil.

**Conflicts of interest**

Douglas G. Adler is a Co-Editor-in-Chief of the journal. The article was subject to the journal’s standard procedures, with peer review handled independently of this Editor and his research groups.

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**Supplementary Table 1. Quality assessment of the study with Newcastle-Ottawa scale and Jadad scale**

| Study               | Years | Selection | Comparability | Outcome |
|---------------------|-------|-----------|---------------|---------|
| Caillol et al.      | 2012  | **        | *             | ***     |
| Choi et al.         | 2019  | **        | *             | ***     |
| Gómez et al.        | 2015  | **        | *             | ***     |
| Levy et al.         | 2011  | **        | *             | **      |
| Matsumoto et al.    | 2020  | **        | *             | ***     |
| Paik et al.         | 2016  | **        | *             | ***     |
| Song et al.         | 2012  | *         | *             | ***     |
| Qin et al.          | 2016  | *         | *             | *       |
| Park et al.         | 2016  | **        | *             | ***     |
| Park et al.         | 2015  | **        | *             | ***     |
| Oh et al.           | 2011  | **        | *             | ***     |
| Oh et al.           | 2014  | **        | *             | ***     |
| Gan et al.          | 2005  | **        | *             | ***     |
| DeWitt et al.       | 2016  | **        | *             | ***     |

**Jadad-Oxford scale for RCT**

| Study               | Years | Randomization | Blinding | Withdrawals |
|---------------------|-------|---------------|----------|-------------|
| Moyer et al.        | 2016  | 2             | 2        | 0           |

*: star scoring system with a maximum of 4 stars allowed for selection, 2 for comparability and 3 for outcome; RCT: Randomized controlled trials

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**Supplementary Figure 1.** Study selection process in accordance with the PRISMA guidelines