**ABSTRACT**

**Background** Pancreatitis is the most common adverse event following Endoscopic Retrograde Cholangiopancreatography, despite rectal administration of indomethacin. Spraying of epinephrine on the duodenal papilla has been proposed as an adjunct to rectal indomethacin for reducing post-ERCP Pancreatitis. We performed a meta-analysis of randomized clinical trials for the additional protective effect of spraying of papilla with epinephrine while using rectal indomethacin to reduce post-ERCP Pancreatitis.

**Methods** An electronic database search was conducted in PubMed, Embase, Google scholar and Cochrane for eligible prospective, randomized studies. The primary outcome comparison of incidence of post-ERCP Pancreatitis in the combination (rectal indomethacin+epinephrine spraying of papilla) vs. control (indomethacin alone) groups, Pooled proportions (%) were calculated using random effects model and I2 statistic was used to assess heterogeneity among studies.

**Results** A total of 2243 patients (mean age 57.54 years; 52.2% females) were included from three prospective, randomized studies that met the inclusion criteria and in investigated the effect of using a combination of epinephrine spraying with rectal Indomethacin on post-ERCP Pancreatitis. The incidence of post-ERCP Pancreatitis was comparable between the combination and control groups (pooled OR: 1.15, CI: 0.58-2.28, p=0.70). There was no statistically significant difference between the two groups in terms of severity of post-ERCP Pancreatitis, or rates of difficult or failed cannulation, pancreas duct cannulation, biliary stricture, precut sphincterotomy, or balloon sphincteroplasty (P>0.05).

**Conclusions** This systematic review and meta-analysis of more than 2000 patients demonstrates a lack of added benefit for the papillary spraying of epinephrine beyond the use of rectal indomethacin to prevent post-ERCP Pancreatitis.

**INTRODUCTION**

Endoscopic Retrograde Cholangiopancreatography (ERCP) is the preferred modality for treating diverse biliary conditions including choledocholithiasis, bile leaks, and strictures [1, 2, 3]. Post-ERCP pancreatitis (PEP), with an incidence of around 2-10% is one of the most common adverse effects of ERCP, resulting in a healthcare cost of over $200 million annually and has a significant morbidity and mortality [1, 4, 5, 6].

Rectal administration of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), such as indomethacin and diclofenac, has been used in high risk patients as chemoprophylaxis agents to reduce the incidence of PEP [7, 8]. Despite the use of rectal NSAIDs, the incidence of PEP remains high. Multiple interventions have been investigated to further reduce the risk of PEP. These include pancreatic duct stenting, aggressive hydration with lactated Ringers solution, and papillary epinephrine spraying [9]. A combination of these methods along with rectal NSAIDS has been proposed as well, but definitive clinical data are lacking.

Spraying of epinephrine on the duodenal papillary mucosa is postulated to reduce PEP by causing arteriolar vasoconstriction, thereby decreasing the edema and improving pancreatic ductal outflow during ERCP. 2 Randomized Controlled Trials (RCT) have demonstrated that spraying of epinephrine causes relaxation of the sphincter of Oddi and reduction of papillary edema by decreasing capillary permeability which prevents PEP [10, 11]. While Epinephrine spraying is inexpensive and convenient, its action lasts less than 5 minutes [12]. A network meta-analysis which evaluated 16
pharmacological agents found that topical epinephrine and rectal NSAIDs are the most effective agents to prevent PEP [13]. Multiple RCT have compared a combination of NSAIDs and epinephrine spray to using NSAIDs alone. Since the studies demonstrated varying results, we conducted a systematic review of existing literature and meta-analysis to assess the benefit of epinephrine spraying in addition to using rectal NSAIDs.

**METHODS**

This systematic review was performed in accordance with Cochrane Handbook for Systematic Reviews of Interventions [14]. It is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

**Search Strategy**

We conducted a comprehensive search of several databases (MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews) from each database’s earliest inception to January 31st, 2019 for relevant articles reporting outcomes of PEP using rectal NSAIDs and epinephrine spraying of the duodenal papilla. An experienced medical librarian helped with the literature search using inputs from the study authors.

Briefly, the search was performed using a combination of keywords including ‘ERCP’, ‘Post ERCP pancreatitis’, ‘rectal NSAIDs’, ‘Indomethacin’, ‘epinephrine spraying’, ‘pancreatitis’. The search was restricted to studies in human subjects published in English language. The title and abstract of the identified studies were independently reviewed by two authors (CSD, AD) and studies not pertinent to the research question were excluded based on pre-specified inclusion and exclusion criteria. The full text of remaining articles was reviewed to determine if they were relevant to the research question. Any discrepancy in article selection was resolved by consensus, and in discussion with the senior author (DK). In addition, we manually searched the bibliographies of selected studies, conference proceedings from major gastroenterology meetings and other review articles on the topic for additional relevant studies.

**Inclusion and Exclusion Criteria**

All RCT that met the following inclusion criteria were included in this meta-analysis:

1. Study population consisting of patients undergoing ERCP who were randomized into rectal NSAIDs alone or combination group of NSAID and epinephrine spraying
2. Reported outcomes of PEP,
3. Sample size of 150 patients or more
4. Studies that mentioned the severity of PEP.

The following studies were excluded:

1. Observational or non-randomized studies
2. Studies where detailed data could not be obtained
3. Letters to the editor, case reports, editorials and review articles.

If multiple publications were identified from the same cohort, only data from the most recent comprehensive report were included.

**Data Extraction and Quality Assessment**

After identifying relevant studies, two authors (CSD and AD) independently extracted data on study characteristics, patient characteristics, and relevant study outcomes (incidence of PEP, and severity of PEP) onto a standardized form. The quality of the individual studies was assessed using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials [16].

**Outcomes Assessment**

The primary outcome of this meta-analysis was to compare the incidence of PEP in the combination (indomethacin+epinephrine) group versus the control (indomethacin alone) group. Secondary outcomes were to compare the severity of pancreatitis between the 2 groups. Severity of pancreatitis was classified as mild, moderate and severe based on the Cotton criteria and the Atlanta classification [4, 17]. The incidence of moderate severe pancreatitis was pooled for statistical analysis. Other outcomes included difficult/failed cannulation, suspected Sphincter of Oddi dysfunction (SOD), pancreatic duct cannulation, presence of biliary strictures, need for precut sphincterotomy, balloon dilation of the sphincter, and number of high-risk patients in both groups.

**Statistical Analysis**

Using the random-effects model described by DerSimonian and Laird [18], we calculated the pooled rates of PEP and 95% Confidence Intervals (CIs). Heterogeneity between study-specific estimates was assessed using inconsistency index (I² statistic), which estimates the proportion of total variation across studies that is related to heterogeneity rather than by chance. Values of <30%, 30%-60%, 61%-75%, and >75% were considered suggestive of low, moderate, substantial, and considerable heterogeneity respectively [19]. Statistical software review manager 5.3 was used to perform statistical analysis and P value <0.05 was considered statistically significant.

**RESULTS**

A total of 1464 citations describing PEP were initially selected, of which 67 studies assessed rectal NSAIDs. Fifteen studies described epinephrine spraying and 5 studies combined epinephrine and rectal NSAIDs (Figure 1). We identified three RCTs [20, 21, 22], reporting the outcomes of PEP and its severity, which randomized patients into an NSAID group and a combination group (NSAIDs+Epinephrine).
Characteristics of Included Studies

All 3 inclusion studies were RCT and included one single centre [20] and two multi-centre studies [21, 22] (Table 1). One study was conducted simultaneously in the United States and India [21], and the other two were done in China [20, 22]. The pooled data had 2243 patients in both groups with 1111 patients (mean age 58 years; females 53.2%) in the combination group and 1132 patients in the control group (mean age 57.05 years, 51.4% females).

The definition of PEP varied across all the included studies. Kamal et al. diagnosed PEP based on characteristic abdominal pain, and elevation of amylase or lipase beyond three times the upper limit of normal, or prolongation of hospital stay for at least 2 days [21]. In the study by Luo et al., PEP was diagnosed when patients had abdominal pain with elevation of amylase to three times the upper limit of normal with hospitalization for at least 2 nights [22]. Hatami et al. defined PEP as amylase level of more than three times the upper limit of normal with at least 2 clinical features of pancreatitis such as abdominal pain or tenderness, nausea, vomiting or backache [20].

Rectal indomethacin was the only NSAID used and at the same dose (100 mg) in all three studies. It was administered immediately after the procedure in studies done by Kamal et al. and Hatami et al. [20, 21], whereas Luo et al. administered it 30 minutes prior to ERCP [22]. The dose of epinephrine was similar in the studies done by Kamal et al. and Luo et al. where 20 ml 0.02% epinephrine was sprayed across the major papilla and the adjacent duodenal mucosa [21, 22]. Hatami et al. however, used 10 ml of 0.01% epinephrine spray [20].

Quality Assessment

Supplementary Figure 1 shows results of risk of bias tool for inclusion studies. All inclusion randomized trials had low risk of bias for random sequence generation and allocation concealment parameters suggesting low risk of selection bias. However, selective reporting of any outcome or presence of any other source of bias was not clarified. Blinding of participants and investigator assessing the outcomes were reported clearly by all but one study [20]. Rate of attrition of initially enrolled subjects was low except Hatami et al. where almost 1/3rd of participants were excluded due to ineligibility [20].

Outcomes

The primary outcome was the incidence of PEP with a combination rectal Indomethacin and epinephrine spraying compared to rectal indomethacin alone. The incidence of PEP was similar in the combination and the control groups (OR 1.15, 95% CI 0.57-2.29, p=0.70; I²=63% (Figure 2A)).

Among the secondary outcomes, there was no statistically significant difference between the two groups in terms of severity of PEP. The incidence of mild PEP (OR 1.09, CI 0.58-2.06 p=0.78), and moderate and severe PEP (OR 1.73, CI 0.76-3.95, p=0.19) were comparable between the combination and control groups (Figure 2B and 2C, respectively).

The occurrence of difficult and/or failed cannulation was similar in the 2 groups (pooled OR 1.05; 95% CI 0.73-1.49, p=0.8). Other secondary outcomes were similar in the 2 groups including proportion of patients with suspected SOD (OR 1.59, 95% CI 0.78-3.23, p=0.2); rate of pancreas duct cannulation (OR 1.08, 95% CI 0.61-1.9, p=0.79); rate of biliary stricture (pooled OR 1.92, 95% CI 0.51-7.21, p=0.34); rate of precut sphincterotomy (OR 1.08, 95% CI 0.85-1.38, (p=0.52); 7) and balloon sphincteroplasty (OR 0.72, 95% CI 0.46-1.13, p=0.15) (Figures 3 and 4; Supplementary Table 1).
Table 1. Baseline characteristics of the studies and patient populations.

<table>
<thead>
<tr>
<th>Study/Year of publication</th>
<th>Centers/ location</th>
<th>Age (Years; mean±SD)</th>
<th>Male (%)</th>
<th>Total patients</th>
<th>Combination group</th>
<th>Control group</th>
<th>Patients with PEP (Treatment/control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hatami et al. 2018(20)</td>
<td>Single center/ Asia</td>
<td>59.06 ± 16.04</td>
<td>66</td>
<td>192</td>
<td>58</td>
<td>68</td>
<td>0/6</td>
</tr>
<tr>
<td>Kamal et al. 2019(21)</td>
<td>Multi-center/ North America and India</td>
<td>52.1 ± 15.6</td>
<td>72</td>
<td>960</td>
<td>477</td>
<td>482</td>
<td>32/31</td>
</tr>
<tr>
<td>Luo et al. 2018(22)</td>
<td>Multi-center/ Asia</td>
<td>61</td>
<td>52</td>
<td>1158</td>
<td>576</td>
<td>582</td>
<td>49/31</td>
</tr>
</tbody>
</table>

Figure 2. Incidence of post ERCP pancreatitis overall (A) and based on severity (B – mild and C – moderate to severe) in the intervention and control group.

Figure 3. Incidence of difficulty/failed cannulation [A], suspected sphincter of Oddi dysfunction [B] and Pancreas duct cannulation [C] in the combination and control group.
DISCUSSION

We performed a systematic review to summarize the currently available information on the use of papillary epinephrine spray in addition to use of rectal indomethacin in the prevention of PEP. The results of our meta-analysis demonstrate that adding epinephrine spray does not provide any additive effects in prevention of PEP when compared to rectal indomethacin alone. In fact, one of the studies included in our meta-analysis reported an increased incidence of PEP in the combination group [22].

PEP is the most common adverse event of ERCP resulting in substantial morbidity and mortality [23, 24]. The reported incidence of PEP varies in different studies depending on the definition, patient selection and procedure related factors. As a result, individual reporting of the incidence of PEP have ranged between 1% to 16% [25, 26]. On the other hand, few large scale trials have cited the incidence of PEP around 3% to 5% [26, 27]. A recent meta-analysis of 21 prospective studies reported the incidence of PEP of approximately 3.5% [1].

Pancreatic injury during ERCP is postulated to occur due to multiple intra-procedural mechanisms including mechanical, thermal, chemical, hydrostatic, enzymatic causes [28]. Local trauma caused by prolonged manipulation, difficult cannulation and repeated instrumentation, use of electrocautery, contrast agents, manometry catheters as well as any foreign materials, can cause papillary edema and activate the proteolytic enzyme resulting in pancreatitis. Activation of the inflammatory cycle by bacterial translocation during ERCP can also cause PEP [28, 29, 30, 31, 32].

Preventive measures are aimed at countering the mechanisms mentioned above in order to reduce the incidence of PEP and alleviate its extent of pancreatic injury. Some of the measures have utilized anti-secretory agents, anti-inflammatory agents or sphincter relaxants. Administration of rectal NSAID, such as indomethacin or diclofenac, is one such intervention which is effective in decreasing the risk of PEP [7]. Several alternatives or supplementary agents have been advocated in the published literature. Multiple studies have reported the benefits of using sublingual or trans-dermal nitrates, but it was not supported by a randomized, controlled study [33]. Similarly, a meta-analysis by Cao et al., showed that Allopurinol has no beneficial effect in preventing PEP [34]. Lately, there has been an on-going debate over the use of papillary epinephrine spray as an alternate or a supplementary measure to fulfil the same purpose, but consensus is lacking.

A study by Matsushita et al. in 470 patients compared the incidence of PEP with papillary spraying of epinephrine alone vs. saline alone. The investigators reported a slightly lower incidence of PEP with epinephrine alone, but the results were not statistically significant [10]. Similar study by Xu et al. in 940 patients showed that epinephrine spraying may be effective but not statistically significant [11].

The strength of the study includes the stringent inclusion criteria which restricted included studies to RCT. This meta-analysis includes a diverse set of large number of patients from various countries which increases the applicability of the results. A previously published meta-analysis of RCT by Laoveeravat and colleagues also...
assessed the efficacy of combining Indomethacin with papillary spray of epinephrine [35]. However, that limited analysis was a letter to the editor which did not assess the quality of the individual studies and failed to report significant discrepancies in the individual studies such as the varying definition of primary outcome of PEP or the differences in the dosing of epinephrine. These limitations preclude our ability to draw sanguine conclusions from the analysis [35]. To the best of our knowledge, this is the only systematic review and meta-analysis comparing a combination of papillary epinephrine sprays with rectal indomethacin vs. rectal indomethacin alone. Since one of the studies reported increased incidence of PEP when compared to other two studies, we can effectively conclude results based on this meta-analysis.

A recently published meta-analysis by Aziz and colleagues also reported similar outcomes [36]. However, we have provided a more rigorous assessment of the individual studies. Specifically, we have highlighted that the variation among the 3 studies in the definition of post-ERCP pancreatitis, as well as the differing timing of the administration of the indomethacin. Further, we have analysed the characteristics of the inclusion studies and provided a detailed explanation of the quality assessment. These are crucial elements of a meticulous analysis. Aziz et al. have commented that outcomes were consistent when fixed effects model and Mantel-Haenzel method was used for pooling the results [36]. To clarify, Mantel-Haenzel method is for analysis of pooled outcomes and fixed or random effect model is for heterogeneity in the outcomes. We have also included clinically important secondary outcomes in our analysis and have attempted to comprehensively interpret the results.

Our study is limited by the relatively small number of randomized clinical trials evaluating the proposed outcomes. However, the study has pooled the data for a significant number of patients which provide a reasonable estimate for the applicability of our results. Further, we were not able to risk-stratify the control and the combination groups since the relevant data was only available in two of our studies. Previous studies and meta-analysis evaluating the use of rectal indomethacin alone have been able to categorize the patients into high-risk vs. average risk groups to assess the individualized application of this intervention based upon the risk of PEP [37, 38]. Finally, since one study had not assessed the adverse events in both the groups, it precluded our ability to analyse the data for adverse events. In the two reported studies [21, 22] the rates of post procedure bleeding and arrhythmias were similar in both groups. While pooled relative risk has been reported by Aziz et al. [36], we chose to calculate Mantel-Haenzel Odds ratio of individual outcomes since the individual randomized controlled trials have dissimilarities along with moderate heterogeneity.

Future studies examining the benefit of adjunctive therapies should risk stratify patients to identify high-risk populations, use standard doses of epinephrine which are administered uniformly, and report adverse events. Further, the studies should be performed in academic and non-academic centres to improve generalizability.

**CONCLUSION**

In conclusion, adding papillary epinephrine spray to rectal NSAIDs does not decrease the incidence of PEP. New studies are needed to identify additional therapeutic options to reduce the incidence of PEP, identify the high-risk patients, and focus on other combination methods to reduce incidence of PEP.

**Conflict of Interest Disclosure**

None of the authors have any relevant conflict of interest to report.

**REFERENCES**


