REVIEW ARTICLE

No Added Benefit of Papillary Spraying of Epinephrine over Rectal Indomethacin for Prevention of Post-ERCP Pancreatitis -A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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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 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].

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Abbreviations ERCP Endoscopic Retrograde Cholangiopancreatography; PEP Post ERCP Pancreatitis; NSAIDs Nonsteroidal Anti-Inflammatory Drugs; PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT Randomized Controlled Trials; SOD Sphincter of Oddi dysfunction; CIs Confidence Intervals; I^2 Inconsistency Index
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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 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 and 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 (I^2 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).

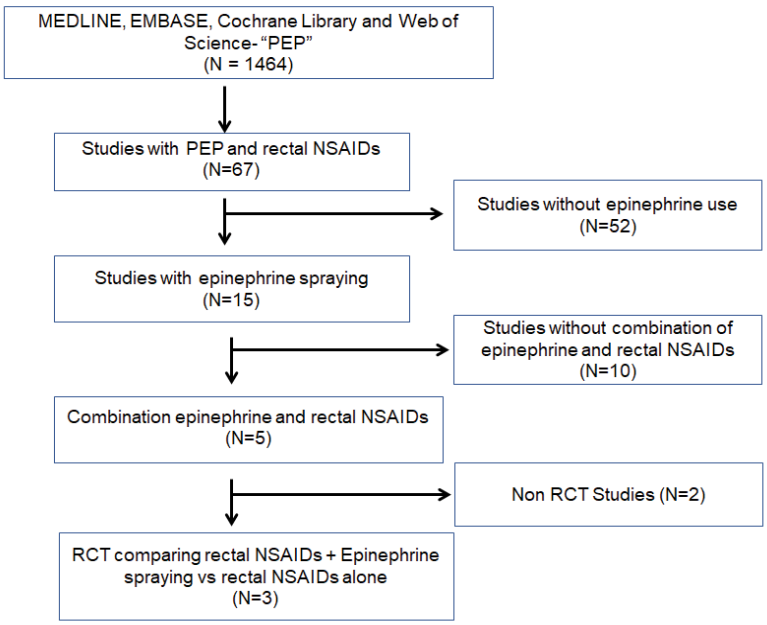

Figure 1. Search Criteria and selection of studies.

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; I^2=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.

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

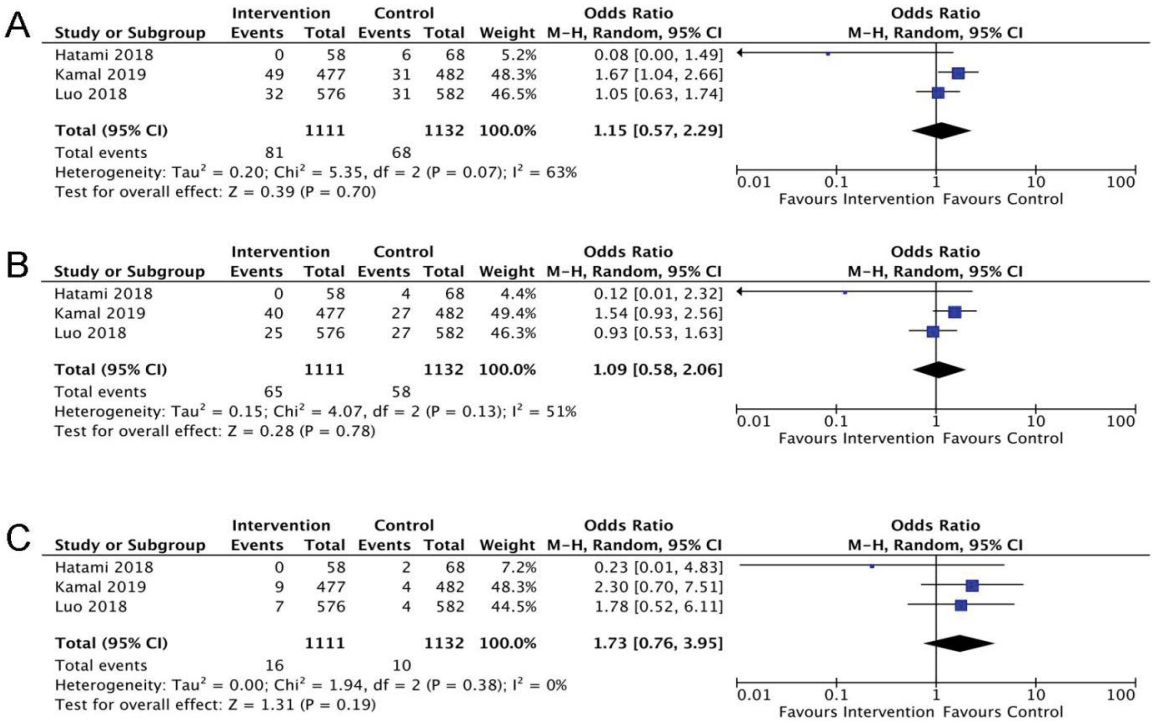

Figure 2. Incidence of post ERCP pancreatitis overall (A) and based on severity (B – mild and C – moderate to severe) in the intervention and control group.

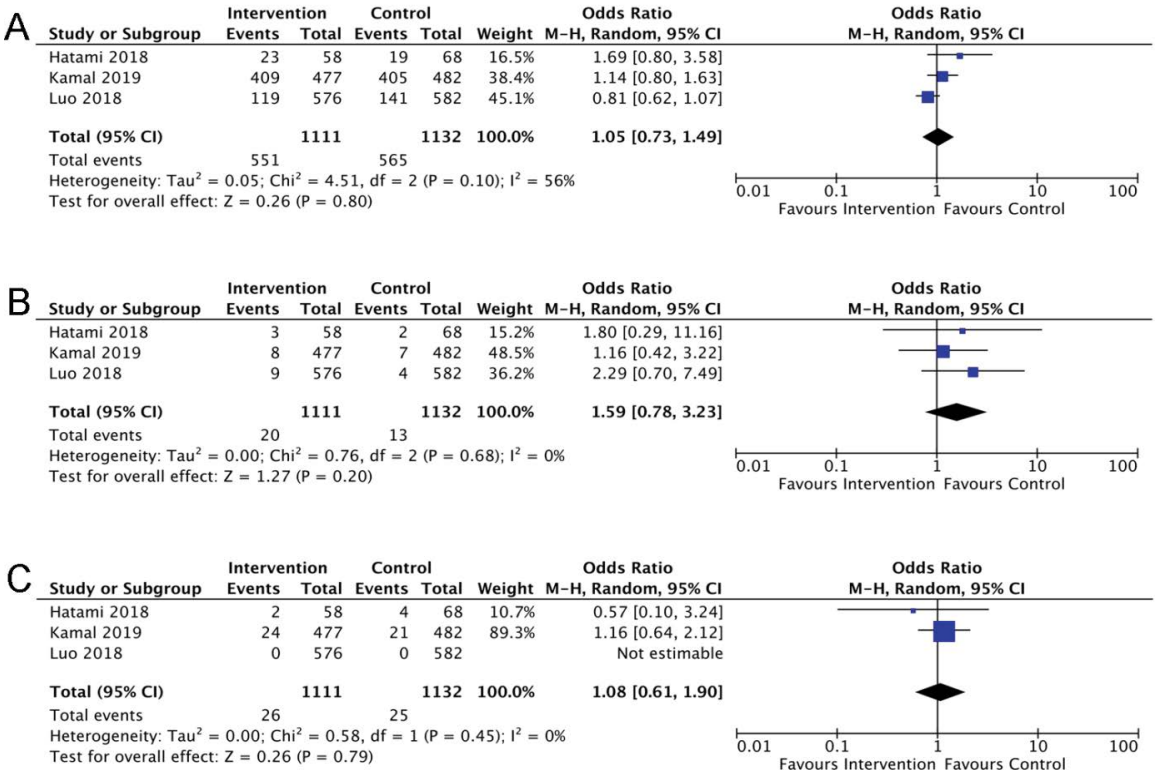

Figure 3. Incidence of difficulty/failed cannulation [A], suspected sphincter of Oddi dysfunction [B] and Pancreas duct cannulation [C] in the combination and control group.

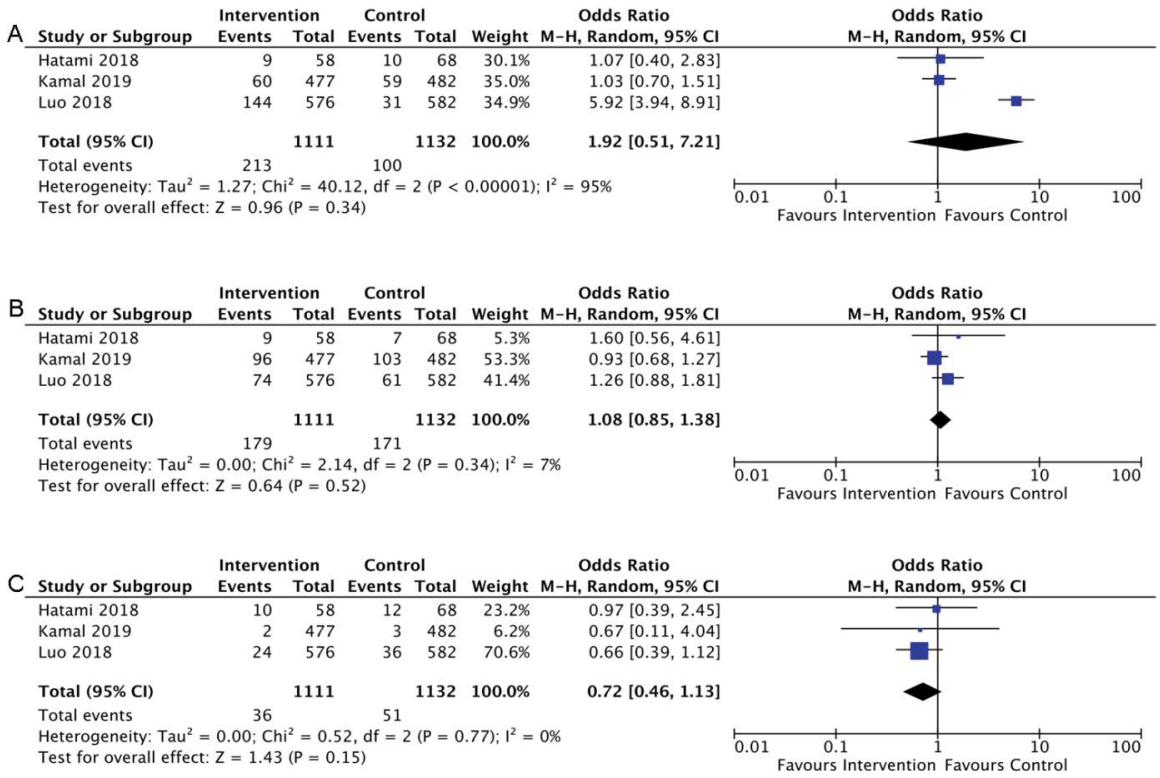

Figure 4. Rate of biliary strictures [A], precut sphincterotomy [B] and Balloon dilation of sphincter [C] in the combination and control group.

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

1. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol 2007; 102:1781-1788. [PMID: 17509029]

2. Kohli DR, Harrison ME, Mujahed T, Fukami N, Faigel DO, Pannala R, et al. Outcomes of endoscopic therapy in donation after cardiac death liver transplant biliary strictures. HPB (Oxford) 2019; S1365-182X(19)30758-0. [PMID: 31676256]

3. Sachdev A, Kashyap JR, D'Cruz S, Kohli DR, Singh R, Singh K. Safety and efficacy of therapeutic endoscopic interventions in the management of biliary leak. Indian J Gastroenterol 2012; 31:253-257. [PMID: 23108722]

4. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991; 37:383-393. [PMID: 2070995]

5. Elmunzer BJ, Waljee AK, Elta GH, Taylor JR, Fehmi SMA, Higgins PDR. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. Gut 2008; 57:1262-1267. [PMID: 18375470]

6. Kochar B, Akshintala VS, Afghani E, Elmunzer BJ, Kim KJ, Lennon AM, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. Gastrointest Endosc 2015; 81:143-149. [PMID: 25088919]

7. Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012; 366:1414-1422. [PMID: 22494121]

8. Luo H, Zhao L, Leung J, Zhang R, Liu Z, Wang X, et al. Routine pre-procedural rectal indometacin versus selective post-procedural rectal indometacin to prevent pancreatitis in patients undergoing endoscopic retrograde cholangiopancreatography: a multicentre, single-blinded, randomised controlled trial. Lancet 2016; 387:2293-2301. [PMID: 27133971]

9. Elmunzer BJ. Reducing the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis. Dig Endosc 2017; 29:749-757. [PMID: 28636774]

10. Matsushita M, Takakuwa H, Shimeno N, Uchida K, Nishio A, Okazaki K. Epinephrine sprayed on the papilla for prevention of post-ERCP pancreatitis. J Gastroenterol 2009; 44:71-75. [PMID: 19159075]

11. Xu LH, Qian JB, Gu LG, Qiu JW, Ge ZM, Lu F, et al. Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis by epinephrine sprayed on the papilla. J Gastroenterol Hepatol 2011; 26:1139-1144. [PMID: 21392105]

12. Ohno T, Katori M, Nishiyama K, Saigenji K. Direct observation of microcirculation of the basal region of rat gastric mucosa. J Gastroenterol 1995; 30:557-564. [PMID: 8574325]

13. Akshintala VS, Hutfless SM, Colantuoni E, Kim KJ, Khashab MA, Li T, et al. Systematic review with network meta-analysis: pharmacological prophylaxis against post-ERCP pancreatitis. Aliment Pharmacol Ther 2013; 38:1325-1337. [PMID: 24138390]

14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.0. Cochrane 2019.

15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151:264-269. [PMID: 19622511]

16. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ 2011; 343:d5928. [PMID: 22008217]

17. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013; 62:102-111. [PMID: 23100216]

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177-188. [PMID: 3802833]

19. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011; 64:1294-1302. [PMID: 21803546]

20. Hatami B, Kashfi SMH, Abbasinazari M, Nazemalhosseini Mojarad E, Pourhoseingholi MA, Zali MR, et al. Epinephrine in the Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Preliminary Study. Case Rep Gastroenterol 2018; 12:125-136. [PMID: 29805355]

21. Kamal A, Akshintala VS, Talukdar R, Goenka MK, Kochhar R, Lakhtakia S, et al. A Randomized Trial of Topical Epinephrine and Rectal Indomethacin for Preventing Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis in High-Risk Patients. Am J Gastroenterol 2019; 114:339-347. [PMID: 30730860]

22. Luo H, Wang X, Zhang R, Liang S, Kang X, Zhang X, et al. Rectal Indomethacin and Spraying of Duodenal Papilla With Epinephrine Increases Risk of Pancreatitis Following Endoscopic Retrograde Cholangiopancreatography. Clin Gastroenterol Hepatol 2019; 17:1597-1606. [PMID: 30391434]

23. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996; 335:909-918. [PMID: 8782497]

24. Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol 2001; 96:417-423. [PMID: 11232684]

25. Barthet M, Lesavre N, Desjeux A, Gasmi M, Berthezene P, Berdah S, et al. Complications of endoscopic sphincterotomy: results from a single tertiary referral center. Endoscopy 2002; 34:991-997. [PMID: 12471544]

26. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009; 70:80-88. [PMID: 19286178]

27. Cheon YK, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, et al. Frequency and severity of post-ERCP pancreatitis correlated with extent of pancreatic ductal opacification. Gastrointest Endosc 2007; 65:385-393. [PMID: 17321236]

28. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 2001; 54:425-434. [PMID: 11577302]

29. Fogel EL, Eversman D, Jamidar P, Sherman S, Lehman GA. Sphincter of Oddi dysfunction: pancreaticobiliary sphincterotomy with pancreatic stent placement has a lower rate of pancreatitis than biliary sphincterotomy alone. Endoscopy 2002; 34:280-285. [PMID: 11932782]

30. Johnson GK, Geenen JE, Johanson JF, Sherman S, Hogan WJ, Cass O. Evaluation of post-ERCP pancreatitis: potential causes noted during controlled study of differing contrast media. Midwest Pancreaticobiliary Study Group. Gastrointest Endosc 1997; 46:217-222. [PMID: 9378207]

31. Pezzilli R, Romboli E, Campana D, Corinaldesi R. Mechanisms involved in the onset of post-ERCP pancreatitis. JOP 2002; 3:162-168. [PMID: 12432182]

32. Sherman S, Hawes RH, Troiano FP, Lehman GA. Pancreatitis following bile duct sphincter of Oddi manometry: utility of the aspirating catheter. Gastrointest Endosc 1992; 38:34-350. [PMID: 1376705]

33. Nøjgaard C, Hornum M, Elkjaer M, Hjalmarsson C, Heyries L, Hauge T, et al. Does glyceryl nitrate prevent post-ERCP pancreatitis? A prospective, randomized, double-blind, placebo-controlled multicenter trial. Gastrointest Endosc 2009; 69:e31-37. [PMID: 19410035]

34. Cao W-L, Yan W-S, Xiang X-H, Chen K, Xia S-H. Prevention effect of allopurinol on post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of prospective randomized controlled trials. PLoS One 2014; 9:e107350. [PMID: 25202907]

35. Laoveeravat P, Perisetti A, Garcia-Saenz-de-Sicilia M, Garg S, Tharian B. Is combining therapy with indomethacin and epinephrine useful for preventing post-ERCP pancreatitis? The answer from a meta-analysis. Eur J Gastroenterol Hepatol 2020; 32:459-460. [PMID: 32011390]

36. Aziz M, Ghanim M, Sheikh T, Sharma S, Ghazaleh S, Fatima R, et al. Rectal indomethacin with topical epinephrine versus indomethacin alone for preventing Post-ERCP pancreatitis - A systematic review and meta-analysis. Pancreatology 2020; 20:356-361. [PMID: 32107191]

37. Inamdar S, Han D, Passi M, Sejpal DV, Trindade AJ. Rectal indomethacin is protective against post-ERCP pancreatitis in high-risk patients but not average-risk patients: a systematic review and meta-analysis. Gastrointest Endosc 2017; 85:67-75. [PMID: 27612923]

38. Thiruvengadam NR, Forde KA, Ma GK, Ahmad N, Chandrasekhara V, Ginsberg GG, et al. Rectal Indomethacin Reduces Pancreatitis in High- and Low-Risk Patients Undergoing Endoscopic Retrograde Cholangiopancreatography. Gastroenterology 2016; 151:288-297. [PMID: 27215656]