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ORIGINAL ARTICLE

Randomized trial of high-dose rectal diclofenac suppository and epinephrine spray on duodenal papilla for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

Background and Aims High-dose rectal diclofenac suppository and epinephrine spray on duodenal papilla during endoscopic retrograde cholangiopancreatography (ERCP) may reduce the incidence of post-ERCP pancreatitis. We performed randomized trial to compare the effect of combination of rectal diclofenac and epinephrine spray on papilla (group A) vs. combination of rectal diclofenac with saline spray (group B) for prevention of post-ERCP pancreatitis.

Methods We performed a double-blind trial at tertiary care center from April 2018 to May 2020 on 882 patients with naive papilla undergoing ERCP. The patients were randomly assigned to groups, A (n=437) or B (n=445). All patients received a single dose of rectal diclofenac 100 mg within 30 minutes before ERCP; 20 mL of diluted epinephrine 0.02% (group A) or saline (group B) was then sprayed on the duodenal papilla at the end of ERCP. The primary outcome was to compare incidence of post-ERCP pancreatitis (PEP) in two groups.

Results The groups had similar baseline characteristics. PEP developed in 28 patients in group A (6.4%) and 35 patients in group B (7.9%) (relative risk, 1.1; 95% CI, 0.87–1.39; p=0.401).

Conclusion Our study showed that addition of epinephrine spray on duodenal papilla did not reduce the risk of post-ERCP pancreatitis. There is need for further studies to evaluate the role of different concentrations of epinephrine spray on papilla for prevention of post-ERCP pancreatitis.

Trial registration Clinical Trials Registry- India (CTRI/2018/04/013396).

Keywords Acute pancreatitis · Duodenal papilla · Endoscopic retrograde cholangiopancreatography · Epinephrine · Gastrointestinal bleeding

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Bullet points of the study highlights

What is already known?

- Post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis is a potentially fatal complication of ERCP. Rectal non-steroidal anti-inflammatory drugs (NSAIDs) and pancreatic duct stenting are known to decrease the raisk of post-ERCP pancreatitis.

What is new in this study?

- Epinephrine spray has been shown to decrease the risk of post-ERCP pancreatitis in a few studies. Our study has robust data to show that epinephrine spray in a concentration of 0.02% did not reduce the risk of post-ERCP pancreatitis.

What are the future clinical and research implications of the study findings?

- There is need for further studies to evaluate different concentrations of epinephrine spray for prevention of post-ERCP pancreatitis.

Introduction

Acute pancreatitis is second most common cause of inpatient gastrointestinal (GI) diagnosis in USA [1]. Its incidence is increasing worldwide as population is becoming overweight, and there is rise in the incidence of gallstones [2, 3]. Due to better understanding of disease and its management, mortality rate has gradually decreased to less than 5% [4]. Acute pancreatitis is clinically defined when patient has 2 out of 3 below mentioned criteria: (a) abdominal pain localized to epigastrium consistent with pancreatic type of pain (b) serum amylase or lipase level greater than three times the upper limit of normal value, and (c) imaging (usually computerized tomography [CT] or magnetic resonance imaging [MRI]) that is consistent with features of acute pancreatitis [5, 6]. Acute pancreatitis is one of the most common and feared complications of endoscopic retrograde cholangiopancreatography (ERCP). It is associated with substantial morbidity and mortality. However, asymptomatic hyperamylasemia occurs in 16.5% to 70% of patients after ERCP [7–9]. Clinical acute pancreatitis develops in 5% of diagnostic ERCPs, 7% of therapeutic ERCPs, and up to 25% in those with suspected sphicter of Oddi dysfunction (SOD) or in those with a history of post-ERCP pancreatitis [10].

Non-steroidal anti-inflammatory drugs (NSAIDs) have shown promising results in decreasing the chances of post-ERCP pancreatitis [11, 12]. It has been recommended that rectal diclofenac or rectal indomethacin should be used prior to ERCP procedure in high-risk patients [11–13]. Other investigators have used multiple agents for prevention of post-ERCP pancreatitis including nitroglycerin [14–16], sprayed lidocaine [17], injected botulinium toxin [18], and nifedipine [19, 20]. But none has been effective in preventing post-ERCP pancreatitis except NSAIDs. Gabexate is a protease inhibitor with anti-inflammatory properties. It has shown some promising results in decreasing incidence of post-ERCP pancreatitis, but is costly and is supported by only a few small trials [21–26]. Octreotide, the analog of somatostatin, has not been effective in decreasing post-ERCP pancreatitis, although there is decrease in post-ERCP hyperamylasemia [27]. Pancreatic duct stent placement clearly decreases the risk of post-ERCP pancreatitis in high-risk patients [28]. Acute pancreatitis after ERCP has been a well-recognized complication with significant morbidity and even mortality [29]. A variety of possible mechanisms have been suggested in the occurrence of pancreatitis, but papillary edema caused by manipulations during cannulation or endoscopic treatment has received the most attention [30, 31]. The papillary edema may cause temporary outflow obstruction of pancreatic juice, and then increase ductal pressure, resulting in the occurrence of pancreatitis. To minimize post-ERCP pancreatitis, epinephrine sprayed on the papilla has been recommended anecdotally in Japan. Ohashi et al. [32] reported that epinephrine sprayed on the papilla prevented pancreatic damage after endoscopic balloon sphincteroplasty. We conducted this randomized trial to assess effect of epinephrine spray on duodenal papilla for prevention of post-ERCP pancreatitis.

Methods

The study was conducted in the Department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar over a period of 2 years (April 2018 to May 2020). Informed consent was taken after properly discussing the procedure of ERCP along with the benefits and complications in the language of the patient. The study was started after getting clearance from the Institutional Ethical Committee.

Study design

Patients older than 18 years, scheduled to undergo therapeutic ERCP with naive papilla at the SKIMS (Department of Gastroenterology) were recruited for the study. Patients were randomized using opaque, sealed envelopes containing random numbers assigning them to undergo a spray of epinephrine (group A) or saline (group B) on the major duodenal papilla during ERCP procedure. Inclusion criteria included the following: age > 18 years, both males and females, signed consent to have proper follow-up as advised. Exclusion criteria included the followings: patients with previous ERCP or biliary/pancreatic stents, acute pancreatitis before ERCP, pregnancy, allergy/contraindications to epinephrine, psychological or medical conditions that would not permit the patient to complete the study or sign the consent form, billroth II or Roux-en-Y anatomy, chronic renal disease (creatinine > 1.5 mg/dL).

At admission to hospital, baseline investigations were done. It included complete blood count, liver function tests, kidney function tests, serum amylase before ERCP, coagulogram, ultrasound abdomen, radiograph chest, and electrocardiogram (ECG). After undergoing ERCP, serum amylase was done at 3 h and 24 h after procedure. Ultrasound of abdomen was also repeated at 24 h after ERCP procedure irrespective of occurrence of abdominal pain. Blood cultures, CT abdomen/MRI abdomen, and other specialized investigations were done as per post-ERCP complications. ERCP procedures were done by endoscopists with at least > 5 years of experience and experience with > 750 ERCP procedures. In control group B, patients received 100 mg of rectal diclofenac suppository 30 minutes before ERCP procedure followed by 20 mL of normal saline sprayed on the duodenal papilla and surrounding regions of edema, over a period of 1 minute using any ERCP cannulation catheter, at the end of ERCP procedure. In experimental group A, patients received 100 mg of diclofenac suppository 30 minutes before ERCP procedure followed by 20 mL of 0.02% epinephrine sprayed on the duodenal papilla and surrounding regions of edema over a period of 1 minute using any ERCP cannulation catheter, at the end of procedure. We followed European Society of Gastrointestinal Endoscopy guidelines for papillary cannulation and sphincterotomy [33]. All patients initially received wire-guided cannulation with a sphincterotome. If cannulation failed, precut sphincterotomy or the double-wire technique was performed at the discretion of endoscopists. Therapeutic manipulation, such as sphincterotomy, balloon dilation, stone extraction, and stenting, was performed if appropriate. During ERCP procedure, parameters like difficult cannulation (>8 attempts), precut sphincterotomy, pancreatic acinarization, pancreatic sphincterotomy, therapeutic biliary sphincterotomy, and controlled radial expansion (CRE) balloon dilatation were noted if done. Pancreatic duct stent placement and post-procedure aggressive hydration with Ringer's lactate solution was not done, as it may reduce the risk of post-ERCP pancreatitis.

Post-ERCP pancreatitis was defined by consensus guidelines as follows: (a) new or increased abdominal pain that is clinically consistent with a syndrome of acute pancreatitis; (b) serum amylase or lipase ≥ 3 times the upper limit of normal value 24 h after the procedure; and (c) hospitalization or prolongation of existing hospitalization for at least 2 days. Severity of post-ERCP pancreatitis was defined using the consensus grading as mild post-ERCP pancreatitis that resulted in hospitalization (or prolongation of existing hospitalization) for ≤ 3 days. Moderate post-ERCP pancreatitis was defined as pancreatitis that resulted in hospitalization (or prolongation of existing hospitalization) for 4–10 days. Severe post-ERCP pancreatitis was defined as pancreatitis that resulted in hospitalization (or prolongation of existing hospitalization) for > 10 days, or led to the development of pancreatic necrosis or pseudocyst, or required additional endoscopic, percutaneous, or surgical intervention [34]. Severity of post-ERCP pancreatitis was also defined using the modified Atlanta criteria as mild post-ERCP pancreatitis if there is no organ failure and no local/systemic complications; moderate post-ERCP pancreatitis if there is organ failure that resolves within 48 h (transient organ failure) and/or local or systemic complications without persistent organ failure; and severe post-ERCP pancreatitis if there is persistent (> 48 h) single or multiple organ failure.

Statistical analysis

An internal audit revealed post-ERCP pancreatitis of approximately 9.8% at our tertiary care institute in patients receiving 50 mg of rectal diclofenac suppository before ERCP procedure. We assumed a reduction of 50% in incidence of post-ERCP pancreatitis, from 9.8% in the placebo group to 4.9% in patients receiving drug (epinephrine spray on papilla). The minimum sample size of 437 per group was calculated on the basis of Fisher's exact test, with a two-sided significance level of 0.05% and 80% power of study. The recorded data were compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of Statistical Package for the Social Sciences (SPSS) Version 20.0 (SPSS Inc.; Chicago, IL, USA). Continuous variables were expressed as mean±SD, and categorical variables were summarized as frequencies and percentages. Graphically the data were presented by bar and pie diagrams. Student's *t*-test was employed for comparing continuous variables. Chi-square or Fisher's exact test, whichever appropriate, was applied for

comparison of categorical variables. A *p*-value of less than 0.05 was considered statistically significant. All *p*-values were two tailed and results were presented as relative risk (RR) with 95% confidence intervals (CI).

End points

Primary end point

1. Effect of epinephrine spray on duodenal papilla for prevention of post-ERCP pancreatitis.

Secondary end points

1. Compare epinephrine group with control group on incidence of hyperamylasemia and adverse events.

Results

A total of 997 patients were enrolled; 115 patients were excluded; 63 did not fulfill the inclusion criteria; 21 declined to participate; 31 had early discharge from hospital before 24 h of procedure. A total of 437 patients were allocated to group A and 445 patients to group B (Fig. 1). Patients of group A (epinephrine group), in addition to rectal diclofenac suppository, received spray of 0.02% epinephrine on papilla during ERCP, while patients of group B (placebo group), in addition to rectal diclofenac suppository, received spray of normal saline on duodenal papilla during ERCP.

The mean age of patients was 48.3±15.6 years in group A and 50.3±16.6 years in group B. Majority of patients in both groups were in the age group of 40–49 years. Female patients comprised 56.1% in group A and 58.9% in group B. Choledocholithiasis was the most common condition, followed by biliary and pancreatic malignancies and recurrent pyogenic cholangitis as indication for ERCP procedure (Table 1).

The patients of two groups were compared regarding difficult cannulation (> 8 attempts), precut sphincterotomy, pancreatic acinarization, pancreatic sphincterotomy, therapeutic biliary sphincterotomy, and CRE balloon dilatation. There was no significant statistical difference between patients of two groups regarding abovementioned characteristics of

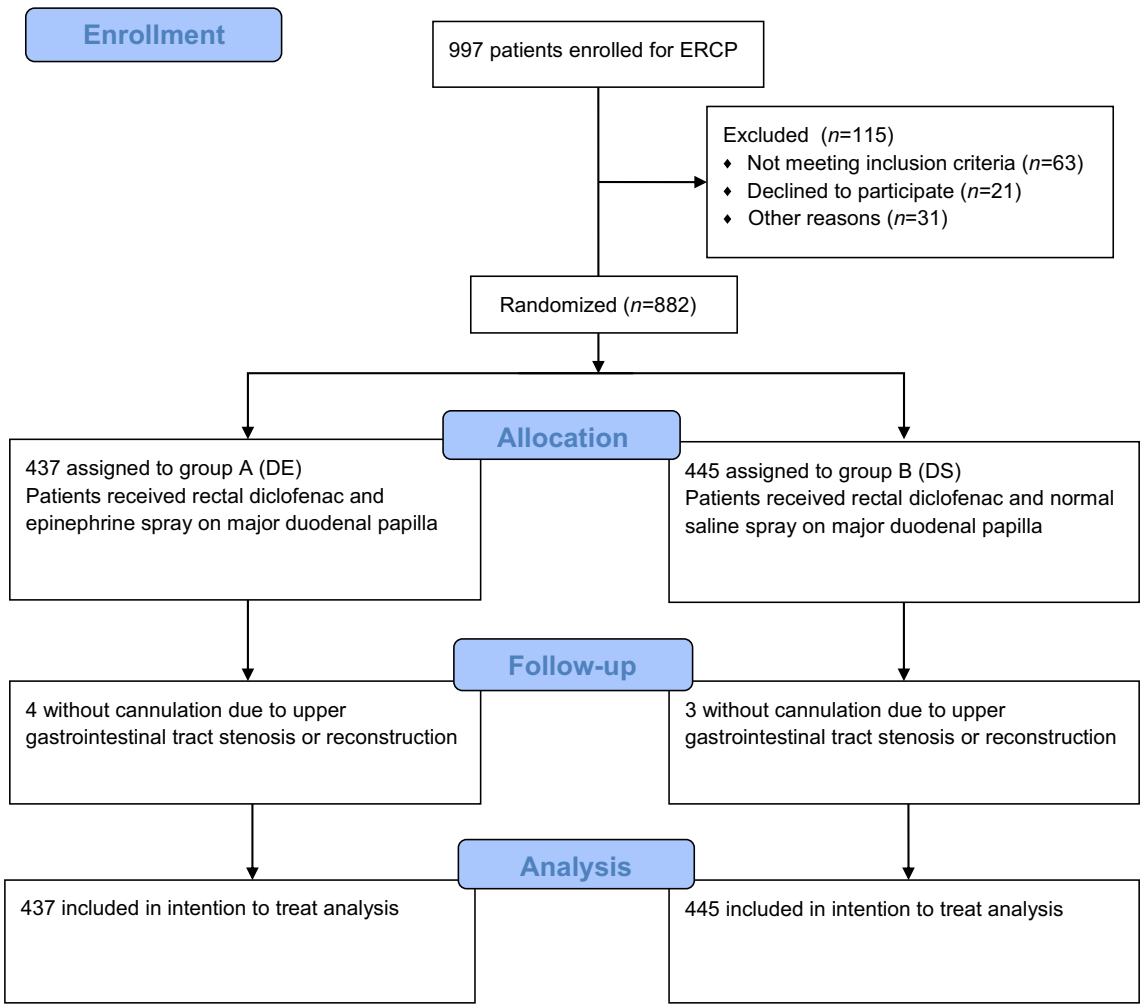


Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram. *ERCP* endoscopic retrograde cholangiopancreatography

Table 1 Pre-endoscopic retrograde cholangiopancreatography diagnosis

Diagnosis	Group A-DE (*n*=437)	Group B-DS (*n*=445)
Bile duct injury	14 (3.2%)	21 (4.7%)
Biliary ascariasis	4 (0.9%)	2 (0.4%)
Choledocholithiasis	101 (23.1%)	113 (25.4%)
Cholelithiasis/choledocholithiasis	156 (35.7%)	137 (30.8%)
Carcinoma gallbladder	23 (5.3%)	16 (3.6%)
Carcinoma head of pancreas	21 (4.8%)	24 (5.4%)
Cholangiocarcinoma	30 (6.9%)	19 (4.3%)
Chronic calcific pancreatitis	18 (4.1%)	32 (7.2%)
Hydatid cyst with intrabiliary rupture	2 (0.5%)	5 (1.1%)
IgG4-related disease	1 (0.2%)	
Pancreatic divisum	2 (0.5%)	
Portal cavernoma cholangiopathy	4 (0.9%)	10 (2.2%)
Recurrent pyogenic cholangitis	61 (14%)	66 (14.8%)
Total	437	445

DE rectal diclofenac and papillary epinephrine spraying group, *DS* rectal diclofenac and papillary saline spraying group

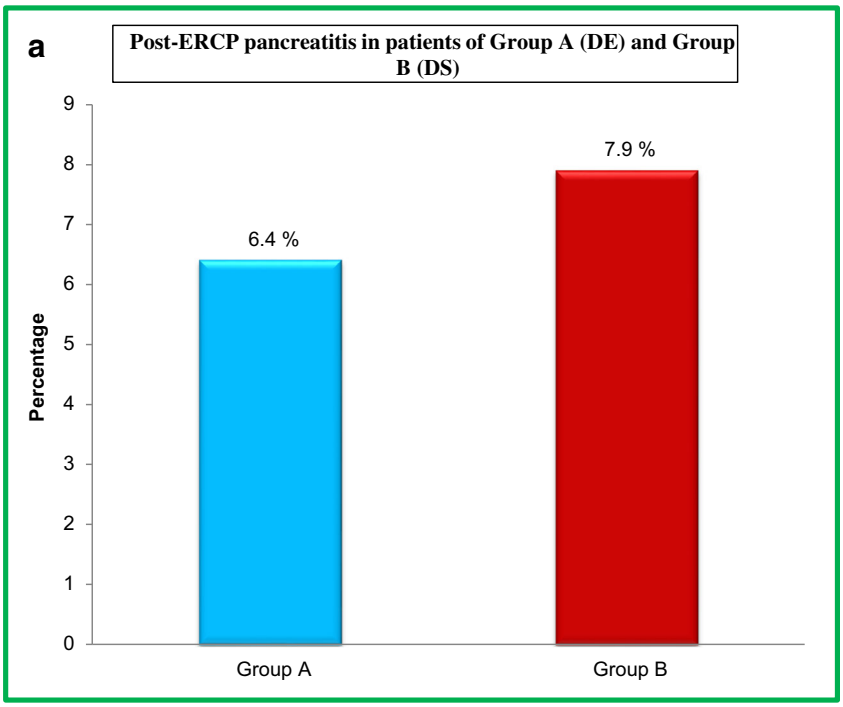
ERCP procedure (p-value > 0.17). During ERCP procedure, difficult cannulation (> 8 attempts), precut sphincterotomy, pancreatic acinarization, pancreatic sphincterotomy, and therapeutic biliary sphincterotomy were done in 28.4%, 9.6%, 5%, 7.3%, and 70.7% patients of group A, while difficult cannulation (> 8 attempts), precut sphincterotomy, pancreatic acinarization, pancreatic sphincterotomy, and therapeutic biliary sphincterotomy were done in 25.4%, 10.8%, 3.8%, 9.9%, and 66.7% patients of group B (Table 2).

In our study the overall incidence of post-ERCP pancreatitis was 7.1%. Twenty-eight patients developed post-ERCP pancreatitis in group A with an incidence of 6.4% (28/437), while 35 patients developed post-ERCP pancreatitis in group B with an incidence of 7.9% (35/445) (Fig. 2a). Although post-ERCP pancreatitis was less in group A patients, who received epinephrine spray on papilla during ERCP than placebo group B (relative risk, 1.1; 95% CI, 0.87–1.39; p-value=0.401), 3.4% had mild pancreatitis; 2.1% had moderate severity, and 0.9% developed severe pancreatitis in group A, while 2.5% developed mild pancreatitis, 4% had moderate pancreatitis, and 1.3% developed severe pancreatitis in group B (Table 3). Patients who received epinephrine spray during ERCP had less severe pancreatitis than placebo group, but it was statistically insignificant (p-value= 0.19). In our study, hyperamylasemia (> 2 times the upper limit of normal) was seen in 54.2% and 26.8% patients of group A at 3 h and 24 h after ERCP procedure, while 68.3% and 31.2% patients of group B had hyperamylasemia at 3 h and 24 h after ERCP procedure. The serum amylase at 24 h after ERCP procedure was higher in placebo group B, but it was not statistically significant (p-value > 0.05). Major post-ERCP complications were GI bleeding and post-ERCP sepsis. Gastrointestinal bleeding occurred in 2.1% patients and sepsis developed in 3.2% patients of group A, while 3.4% had GI bleeding and 3.8% developed sepsis in group B (Fig. 2b). In our study GI bleeding was less in group A (epinephrine group) as compared to group B (placebo); however, it was statistically insignificant (p-value > 0.23).

Table 2 Endoscopic retrograde cholangiopancreatography procedure related parameters

	Group A-DE (*n*=437)	Group B-DS (*n*=445)	*p*-value
Difficult cannulation (> 8 attempts)	124 (28.4%)	113 (25.4%)	0.318
Precut sphincterotomy	42 (9.6%)	48 (10.8%)	0.564
Pancreatic acinarization	22 (5%)	17 (3.8%)	0.381
Pancreatic sphincterotomy	32 (7.3%)	44 (9.9%)	0.175
Therapeutic biliary sphincterotomy	309 (70.7%)	297 (66.7%)	0.204
CRE balloon dilatation of biliary sphincter	125 (28.6)	110 (24.7%)	0.192

DE rectal diclofenac and papillary epinephrine spraying group, *DS* rectal diclofenac and papillary saline spraying group, *CRE* controlled radial expansion



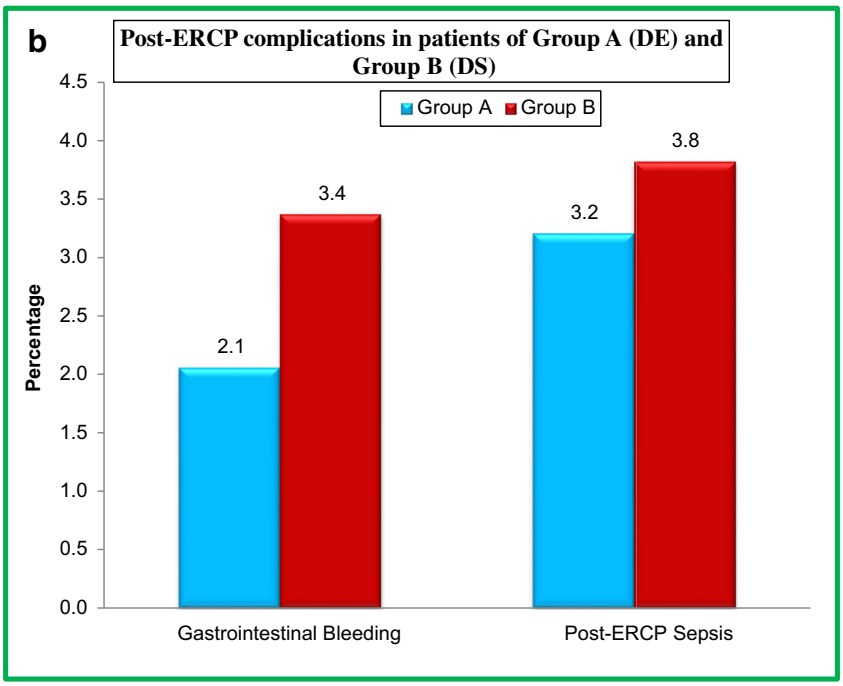


Fig. 2 **a**Post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis occurred in 6.4% patients of group A and 7.9% patients of group B (relative risk, 1.1; 95% CI, 0.87–1.39 and *p*-value of 0.401). **b** Major post-ERCP complications were gastrointestinal bleeding and post-ERCP sepsis. *DE* rectal diclofenac and papillary epinephrine spraying group, *DS* rectal diclofenac and papillary saline spraying group

Discussion

In our study, the overall incidence of post-ERCP pancreatitis was 7.1%. Although post-ERCP pancreatitis was less in group A patients, who received epinephrine spray on papilla during ERCP than placebo group B, it was statistically insignificant (relative risk, 1.1; 95% CI, 0.87–1.39; *p*-value=0.401). Matsushita et al. [35] recruited 370 patients and randomized them to have 10 mL of either 0.02% epinephrine (epinephrine group) or saline (control group) sprayed on the papilla after diagnostic ERCP and prospectively analyzed the occurrence of post-ERCP pancreatitis. Overall, post-ERCP pancreatitis occurred in 4 of the 370 patients (1.1%). The incidence of pancreatitis tended to be higher in the control group (4/185) than in the epinephrine group (0/185) ($p = 0.1230$). They concluded that epinephrine sprayed on the papilla tended to prevent post-ERCP pancreatitis, although it was not statistically significant because of the low incidence of pancreatitis. Xu et al. [36] recruited 941 patients and randomized

Table 3 Severity of post-endoscopic retrograde cholangiopancreatography pancreatitis and complications

	Group A-DE (*n*=437)	Group B-DS (*n*=445)	*p*-value
Incidence of PEP	28 (6.4%)	35 (7.9%)	0.401
Severity of PEP (Cotton's criteria)			
Mild	15 (3.4%)	11 (2.5%)	0.194
Moderate	9 (2.1%)	18 (4%)	
Severe	4 (0.9%)	6 (1.3%)	
Complications			
Gastrointestinal bleeding	9 (2.1%)	15 (3.4%)	0.231
Post-ERCP sepsis	14 (3.2%)	17 (3.8%)	0.619

DE rectal diclofenac and papillary epinephrine spraying group, *DS* rectal diclofenac and papillary saline spraying group, *ERCP* endoscopic retrograde cholangiopancreatography, *PEP* post-endoscopic retrograde cholangiopancreatography pancreatitis

them to have 20 mL of either 0.02% epinephrine or saline sprayed on the papilla after diagnostic ERCP to prevent post-ERCP pancreatitis. Post-ERCP pancreatitis occurred in 40 of the 941 patients (4.25%); the incidence of pancreatitis tended to be higher in the control group (31/480, 6.45%) than in the epinephrine group (9/461, 1.95%) (p = 0.0086). They concluded that epinephrine sprayed on the papilla may be effective to prevent post-ERCP pancreatitis. Our study concluded that addition of epinephrine spray to rectal diclofenac suppository does not reduce risk of post-ERCP pancreatitis; however, there is numerical reduction. In our study, the overall incidence of post-ERCP pancreatitis was higher both in epinephrine group (6.4%) and placebo group (7.9%) than the above-mentioned studies. Possible reasons are different endoscopists did ERCP, unrecognized high-risk patients, and more aggressive ERCP procedures as CRE balloon dilatation of sphincter to remove large common bile duct stones was done in 28.6% patients in epinephrine group A and 24.7% patients of placebo group B.

Hatami et al. [37] randomized 66 patients to the epinephrine group (group A), 68 to the indomethacin group (group B), and 58 individuals to the indomethacin-epinephrine group (group C). Post-ERCP pancreatitis developed in 7 of the 192 individuals (3.6%), 6 post-ERCP pancreatitis occurred in the indomethacin group and 1 in the epinephrine group (p = 0.016). This study concluded that in compared to the administration of indomethacin alone, a single application of epinephrine and the combination of epinephrine and indomethacin seem to be effective in reducing post-ERCP pancreatitis.

Kamal et al. recruited 960 patients in a double-blind multicentric trial of rectal indomethacin alone vs. a combination of rectal indomethacin and topical spray of epinephrine for prevention of post-ERCP pancreatitis in high-risk patients. This study concluded that addition of topical epinephrine did not reduce the incidence of post-ERCP pancreatitis as compared to rectal indomethacin alone [38].

Luo et al. [39] performed a double-blind trial at 10 centers in China, from February 2017 to October 2017 on 1158 patients with native papilla undergoing ERCP. Although the data analysis showed that the incidence of PEP was higher in patients receiving combined prevention compared with indomethacin alone, the statistical difference might not amount to substantial clinical significance. The effect size of this study was pretty low (RR=1.6). The trial was stopped early after one-third recruitment due to the safety concerns and futility. The trial was underpowered to draw an absolute conclusion that the combination therapy increased the risk of post-ERCP pancreatitis. The result of our study is not consistent with it; reasons may be that the above-mentioned study was carried out at 10 different centers and they have used indomethacin before ERCP. In our study, patients received high dose of diclofenac rectal suppository 100 mg rather than indomethacin suppository and the study was carried out at one center. It is also possible that the combination of high-dose diclofenac suppository and epinephrine spray may have different results than indomethacin rectal suppository and epinephrine spray.

In our study, hyperamylasemia (> 2 times upper limit of normal) was seen in 54.2% and 26.8% patients of group A at 3 h and 24 h after ERCP procedure, while 68.3% and 31.2% patients of group B had hyperamylasemia at 3 h and 24 h after ERCP procedure. The serum amylase at 24 h after ERCP procedure was higher in placebo group B, but it was not statistically significant (p-value > 0.05). Christiforidis et al. documented hyperamylasemia in 16.5% of patients after ERCP and He et al. documented hyperamylasemia in 18.3% after ERCP procedures [8, 9]. Ito et al. showed that 38% patients developed post-ERCP hyperamylasemia [40]. Our study does not show any relation of hyperamylasemia at 3 h with subsequent development of post-ERCP pancreatitis.

In our study, major post-ERCP complications were GI bleeding and post-ERCP sepsis. Though GI bleeding was less in group A (epinephrine group) as compared to group B (placebo), it was statistically insignificant (p-value > 0.23).

In conclusion, our study showed that combination of rectal diclofenac and epinephrine spray on duodenal papilla does not reduce the risk of post-ERCP pancreatitis; however, there was a numerical reduction. There is need for further studies to

evaluate the role of different concentrations of epinephrine spray on papilla for prevention of post-ERCP pancreatitis.

Compliance with ethical standards

Conflict of interest HAD, AS, GJ, MAK, BS, NAS, AS, and SM declare that they have no conflict of interest.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human andanimal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

Informed consent Informed consent of patient has been taken for this publication.

Disclaimer The authors are solely responsible for the data and the contents of the paper. In no way, the Honorary Editor-in-Chief, Editorial BoardMembers, the Indian Society of Gastroenterology or the printer/publishers are responsible for the results/findings and content of this article.

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