Efficacy of Epinephrine Injection in Preventing Post-ERCP Pancreatitis

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Background: Rectal indomethacin or a topical spray of epinephrine to the papilla of Vater has each shown efficacy alone in the prevention of post–endoscopic retrograde cholangiopancreatography pancreatitis (PEP). We supposed that a submucosal epinephrine injection would be more effective and longer acting than a topical epinephrine spray and therefore would further reduce the incidence of PEP.

Patients and Methods: A retrospective analysis was conducted of 412 patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) between January 2017 and December 2019. These patients were divided into 2 groups: the indomethacin group and the indomethacin plus the submucosal epinephrine injection group. The incidence rates and severity of PEP, post-ERCP hyperamylasemia, other outcomes, and any other adverse events were compared between the groups.

Results: Baseline demographic and clinical characteristics and procedure-related parameters were similar between the 2 groups. The incidence of PEP was 0.4% in the epinephrine group compared with 5.1% in the indomethacin group ($P < 0.001$). Post-ERCP hyperamylasemia occurred in 24.6% of patients in the indomethacin group, whereas 7.6% of patients in the epinephrine group developed this condition; the difference was significant ($P < 0.001$). Post-sphincterotomy bleeding occurred in 5 patients, all of whom were in the indomethacin group ($P < 0.001$). Other adverse events, including arrhythmias, acute coronary events, stroke, or hypertension were not significantly different between the 2 groups.

Conclusion: Addition of a submucosal epinephrine injection in conjunction with rectal indomethacin significantly reduced the incidence of PEP, post-ERCP hyperamylasemia, and post-sphincterotomy bleeding.

Key Words: ERCP, post-ERCP pancreatitis, epinephrine hyperamylasemia, indomethacin

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Post–endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is the most common major complication following endoscopic retrograde cholangiopancreatography (ERCP). It occurs in 3% to 9% of average-risk patients and in up to 15% to 20% of those at high risk.[1–3]

Despite its 40-year history, the incidence of PEP has not been significantly reduced. Although most cases are mild, PEP is directly caused by clinicians themselves, which makes its course difficult to predict. For this reason, PEP remains a major concern for endoscopists.

Because of the importance of this issue, several drugs have been evaluated to determine their role in the prevention of PEP; however, the results have largely yielded insufficient outcome data.[4–6] Although several drugs have shown somewhat potential effectiveness, including somatostatin,[7] gabexate mesylate,[8] ulinastatin,[9] glyceryl trinitrate,[10] heparin,[11] and interleukin,[12] many of these medications are costly, demanding, or require sophisticated administration, which means that they may not be applicable in daily clinical practice. Given these restrictions, a drug that has minimal side effects and few contraindications and is also easy to use and has an apparent prophylactic effect against PEP is still needed.

Several possible mechanisms for PEP have been suggested, but papillary edema caused by manipulations during cannulation and thermal injury from electrocautery current have received the most attention. Papillary edema may cause temporary outflow obstruction of pancreatic juices and then increase ductal pressure, resulting in PEP.[13]

To minimize PEP, the spraying of epinephrine on the papilla has been recommended by some studies in Japan.[14–17] Akshintala et al[4] performed a systematic review and network meta-analysis (NMA) in 2013 that compared 16 drugs in 99 randomized controlled trials (RCTs). The results of that NMA stated that topical epinephrine sprayed on the papilla of Vater was the best drug, followed by rectal nonsteroidal anti-inflammatory drugs (NSAIDs), although the mechanisms of action of these 2 drugs are different.

There is scarce literature about the duration of action of epinephrine on gastrointestinal mucosal microcirculation. One experimental study reported that the length of action of topical epinephrine on the gastrointestinal mucosa is between 1 and 5 minutes.[18]

Chung and colleagues have reported that epinephrine topically applied to the submucosa has been shown to cause constriction followed by autoregulatory escape (the return of vessel diameters toward normal) of the submucosal arterioles in the rat stomach. Using the laser Doppler flowmetry technique, these authors showed that a submucosal injection of epinephrine caused a dramatic drop in blood flow signals, which did not exhibit any tendency to return to the baseline level for up to 120 minutes.[19]

We have been influenced by Japanese studies and Akshintala and colleagues' meta-analysis and have clinically embraced their techniques; we often administer an epinephrine injection around the papilla of Vater during ERCP procedures. This is an empirical procedure; there is no evidence that this practice reduces the incidence of PEP, but we hope that if epinephrine is injected into the submucosal layer around the papillae instead of being sprayed on the same location, its effect may be longer lasting and may further reduce the chances of developing PEP. We have also

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routinely administered rectal indomethacin in patients with naive papilla based on the findings of earlier studies.[20,21]

The purpose of this hospital-based, case-control retrospective study was to assess whether the combination of NSAIDs and a submucosal epinephrine injection around the papilla of Vater was more effective than NSAIDs alone in preventing PEP.

PATIENTS AND METHODS

We conducted a retrospective cohort study at Duzce University Hospital. The records of patients who underwent ERCP from January 2017 to December 2019 were retrospectively analyzed using prospectively collected and maintained data within an endoscopy database. In total, 613 consecutive patients underwent ERCP in the same endoscopy units, and 412 patients with naive papilla were eligible for study inclusion. We excluded patients whose procedures were terminated because the papilla of Vater could not be reached and also any patients with a earlier history of ERCP with endoscopic biliary sphincterotomy or precut sphincterotomy and preprocedure active pancreatitis.

From January 2017 to June 2018, the patients received rectal indomethacin alone, which was routinely administered following the procedure unless the patient had a contraindication, such as acute kidney injury or active peptic ulcer disease. From June 2018 to December 2019, submucosal epinephrine was injected around the papilla of Vater in addition to administration of rectal indomethacin.

The primary endpoint of this study was the incidence of PEP. The secondary outcome measure was the occurrence of post-ERCP hyperamylasemia.

Endoscopic Procedures

In addition to transabdominal ultrasonography, as all patients with suspected diagnosis were evaluated by computerized tomography, magnetic resonance imaging, or endoscopic ultrasound earlier to ERCP, all patients underwent ERCP with a therapeutic purpose.

All procedures were performed by 1 endoscopist, with experience in ERCP of > 300 ERCP annually and approximately 2500 ERCP in 8 years, using the Olympus Video Duodenoscope (Olympus TJF 240, 4.2-mm working channel; Olympus Corporation; Tokyo, Japan). Before the ERCP procedure, all enrolled patients provided informed consent. Premedication was administered in the form of intravenous midazolam (5 mg) and fentanyl (50 mcg). If necessary, duodenal peristalsis was inhibited using 1 mg intramuscular glucagon subcutaneously instead of hyoscine n-butyl bromide due to the atropine-like adverse effects of this drug. In all patients with naive papilla, cannulation was performed using a standard papillotome (Ultratome; Boston Scientific, Marlborough, MA) loaded with a hydrophilic guidewire (VisiGlide 0.035-inch; Olympus Corporation). During the wire-guided cannulation (WGC), the guidewire was manipulated by an assistant physician or nurse with expertise in ERCP procedures. This WGC technique is the only method routinely used in our clinic; contrast-assisted cannulation is never principally

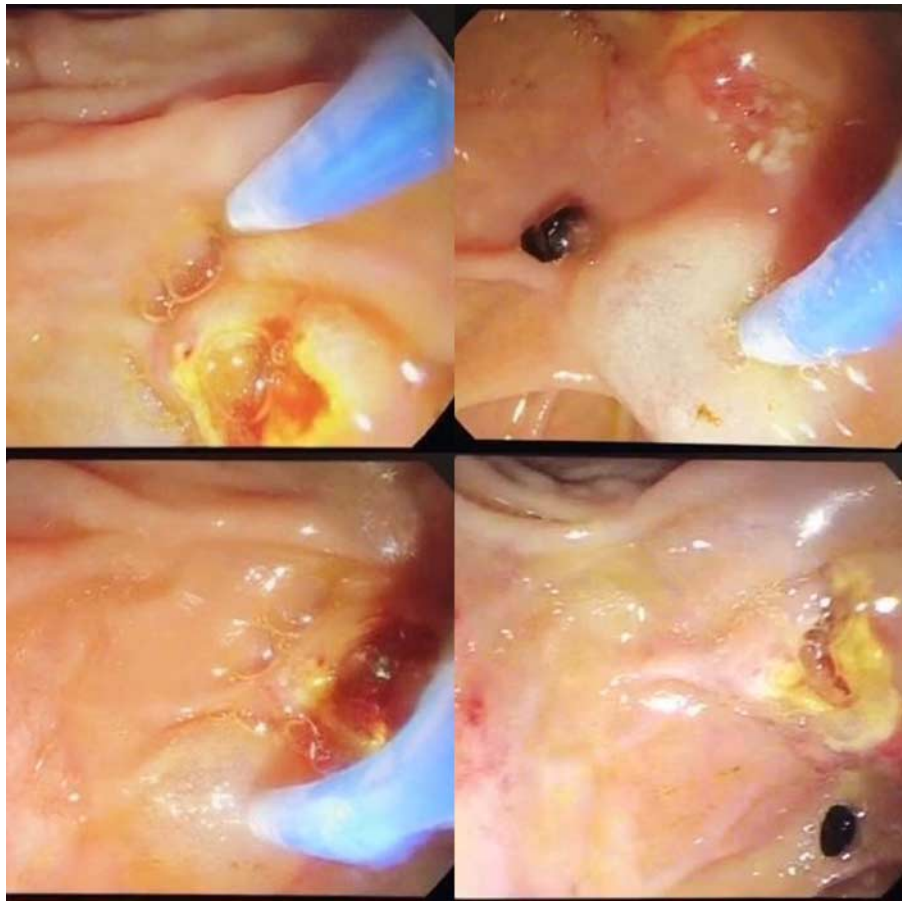

FIGURE 1. Epinephrine injection around the papilla of Vater. full color online

performed. The epinephrine injection was carried out using an endoscopic sclerotherapy needle (Interject, 23-G, 4-mm maximum needle extension length; Boston Scientific). All endoscopic and radiologic data were recorded and maintained using a video recorder system.

Study Design

The patients were divided into 2 groups. The patients in the indomethacin group (n = 203; treated between January 2017 and June 2018) were treated with rectal indomethacin alone. In the epinephrine group (n = 209; treated between June 2018 and December 2019), the 4 quadrants of the peripapillary region were injected with 4 mL of 1:1000 epinephrine (adrenalin 0.5 mg/1 mL ampoule; Drogsan, Istanbul, Turkey) 1 mL in each quadrant 1 to 2 cm away from the papillary orifice (Fig. 1). In this group, 2 mg of epinephrine was injected just before the duodenoscope was removed, and 100 mg rectal indomethacin (Endol Suppository; Deva, Istanbul, Turkey) was applied immediately after removal of the duodenoscope. The blood pressure, pulse rate, and electrocardiography were monitored in all patients both during and after the procedure. All patients were hospitalized for at least 1 night, and the serum amylase and lipase levels were measured before and again at 4 hours after the procedures. Amylase, lipase, and other blood tests were also performed routinely 24 hours after ERCP.

Definitions

Specific complications of ERCP (pancreatitis, cholangitis, bleeding, and perforation) were defined and graded as designated by Cotton et al.[22] PEP was described as at least a threefold increase in amylase levels together with typical abdominal pain 24 hours after the procedure. Post-ERCP hyperamylasemia was defined using normal clinical conditions, but serum amylase levels were elevated above the normal upper limit (100 IU/L) 24 hours after the procedure.

Because of the retrospective design of the study, some parameters, such as the numbers of cannulation attempts, of pancreatic guidewire passages and of failed prophylactic pancreatic stent placements, could not be used due to gaps in some of the data. In cases with > 5 contacts with the papilla of Vater, > 5 minutes of cannulation attempts, or > 1 unintended pancreatic duct cannulation, the procedure was converted to either a precut sphincterotomy or a needle-knife fistulotomy at our center. Therefore, patients who underwent precut sphincterotomy, needle-knife fistulotomy, or the double-guidewire method were included in the difficult cannulation group.

Patients at high risk for PEP and difficult cannulation were defined according to the European Society of Gastrointestinal Endoscopy Guidelines.[23] Written informed consent for the procedure and the use of the collected data were obtained from each patient in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board at our institution (Ethics Committee Decision Number: 2020/60).

Statistical Analysis

The study data were analyzed using the statistical package for the social sciences software, version 20.0 (IBM Corp.). Quantitative parametric data are expressed as the mean with the SD; quantitative nonparametric data are shown as the median with the minimum and maximum. The Kolmogorov-Smirnov test was used to analyze the distribution of variables. The data were compared using the independent-samples *t* test in cases with parametric parameters or using the Mann-Whitney *U* test for nonparametric parameters. χ^2 or Fisher exact tests were applied to compare qualitative data. Univariate and multivariate logistic regression analyses were performed to investigate individual parameter associations with the risk factors for PEP.

RESULTS

From January 2017 through December 2019, 613 total participants were enrolled. Of these, 238 were excluded from further analysis: 201 due to non-naive papilla, 27 because of acute pancreatitis during ERCP, and 7 in whom the papilla of Vater could not be reached. Five additional participants were excluded from the analysis secondary to incomplete medical records (Fig. 2). In total, 209 patients received epinephrine

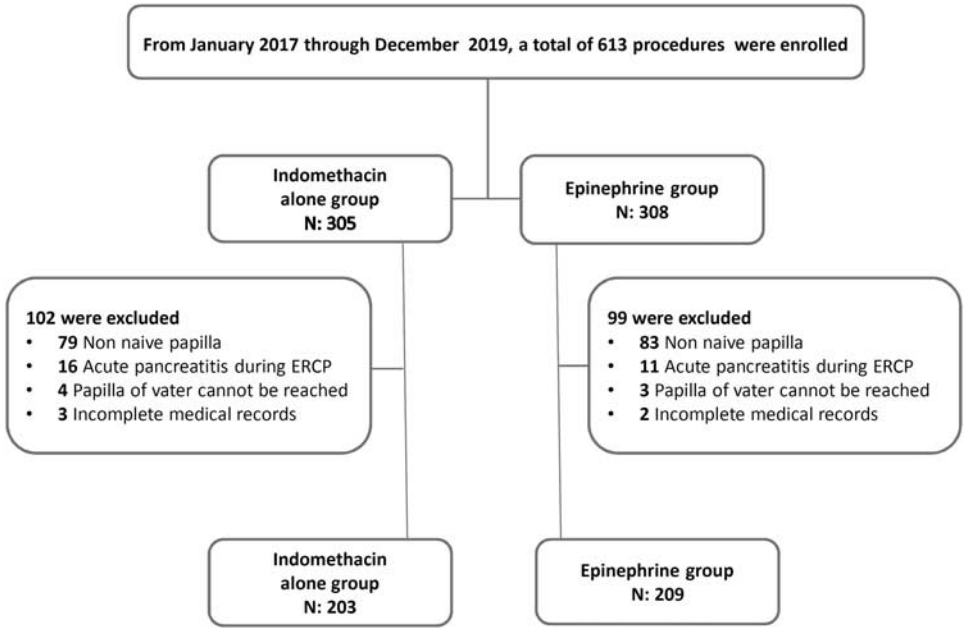

FIGURE 2. Enrollment flowchart of the study participants. ERCP indicates endoscopic retrograde cholangiopancreatography.

injections plus rectal indomethacin (epinephrine group), and 203 patients received rectal indomethacin alone (indomethacin group).

Baseline characteristics and demographic data, including age, sex, pre-ERCP amylase, and lipase levels, were similar in both groups (Table 1). Incidence rates of the patient and procedure-related risk factors for pancreatitis were also similar in both groups; details of the procedures of the study groups are summarized in Table 2. All ERCP procedures were therapeutic, and choledocholithiasis was the most common indication for ERCP

TABLE 1. Baseline Characteristics of Patients

Characteristics	n (%) Epinephrine and Indomethacin Group (N = 209)	Indomethacin Group (N = 203)	*P*
Age (mean ± SD) (y)	60.1 ± 12.1	58.5 ± 11.7	0.658
Female sex,	99 (47.3)	101 (49.7)	0.787
Female, age < 35 y	18 (8.6)	22 (10.8)	0.623
BMI (kg/m2)	23.5 ± 3.7	23.2 ± 3.1	0.974
Inpatient status (%)	100	100	
Smoking			
Yes	42 (20)	40 (19.8)	0.893
Alcohol			
Yes	20 (9.7)	21 (10.2)	0.804
Billroth II	4 (1.9)	5 (2.4)	0.473
History of previous acute pancreatitis	20 (9.6)	17 (8.3)	0.313
History of recurrent pancreatitis	4 (1.9)	3 (1.4)	0.481
Prior history of ERCP	0 (0)	0 (0)	
Prior history of cholecystectomy	52 (24.8)	50 (24.6)	0.929
High-risk patients*	76 (36.3)	71 (34.9)	0.332
Comorbitidies			
Coronary heart disease	20 (9.5)	18 (8.6)	0.284
Heart failure	12 (5.7)	10 (4.9)	0.317
Hypertension	45 (21.5)	40 (19.7)	0.128
Diabetes mellitus	22 (10.5)	24 (11.8)	0.196
Chronic pulmonary disease	15 (7.1)	18 (8.8)	0.179
Cirrhosis	4 (1.9)	3 (1.4)	0.815
Cerebrovascular disease	4 (1.9)	5 (2.4)	0.604
Pre-ERCP laboratory test (mean ± SEM)			
Amylase level (IU/L)	63.7 ± 17.7	68.5 ± 19.5	0.582
Lipase level (IU/L)	71.0 ± 21.3	80.5 ± 17.4	0.426
ALT (U/L)	157 ± 26	179 ± 28	0.374
Total bilirubin (mg/dL)	8.3 ± 2.0	8.4 ± 3.0	0.821
ALP (U/L)	560 ± 73	647 ± 92	0.082
GGT (U/L)	574 ± 81	603 ± 75	0.362
WBC	6.730	6.870	0.904
CRP	2.3 ± 0.9	2.2 ± 0.7	0.992
Hospitalization days	1.3	1.2	0.846

*High-risk state was defined according to European Society of Gastrointestinal Endoscopy (ESGE) Guideline,[23] whose had at least 1 of the following factors: female who are under 35 years of age, suspected sphincter of Oddi dysfunction, difficult cannulation, pancreatic guidewire passages > 1, pancreatic injection, previous pancreatitis, previous post–endoscopic retrograde cholangiopancreatography pancreatitis.

ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; GGT, gamma-glutamyl transferase; WBC, white blood cell.

TABLE 2. Procedure-related Parameters

Characteristics	n (%) Epinephrine and Indomethacin Group (N = 209)	Indomethacin Group (N = 203)	*P*
Therapeutic procedure (%)	100	100	
Targeted duct (%)			
Common bile duct	100	100	
Pancreatic duct	0	0	
Success rate of selective cannulation (%)	98.7	98.2	0.992
Difficult cannulation*	57 (27.2)	58 (28.5)	0.818
Cannulation method†			
Guidewire	209 (100)	203 (100)	
Contrast	0 (0)	0 (0)	
Precut sphincterotomy	3 (1.43)	3 (1.47)	0.986
Needle-knife fistulotomy	25 (11.9)	23 (11.3)	0.972
Double-guidewire technique	9 (4.3)	10 (4.9)	0.881
Transpancreatic septotomy	3 (1.43)	2 (0.98)	0.649
Biliary sphincterotomy	206 (98.5)	199 (98)	0.938
Pancreatic sphincterotomy	0 (0)	0 (0)	
Time to selective deep cannulation (mean ± SD) (min)	6.1 ± 2.1	5.8 ± 1.3	0.683
Total procedure time (mean ± SD) (min)	27.8 ± 10.1	26.1 ± 9.2	0.848
Ampullectomy	7 (3.3)	6 (2.9)	0.459
Balloon dilatation of intact biliary sphincter	0 (0)	0 (0)	
EPBD	11 (5.2)	12 (5.9)	0.835
EPLBD	25 (11.9)	24 (11.8)	0.944
Mechanical lithotripsy	8 (3.8)	7 (3.4)	0.927
Failure to clear bile duct stones	22 (10.5)	23 (11.3)	0.728
Biliary plastic stent	56 (26.7)	57 (28)	0.643
Endoscopic nasobiliary drainage	19 (9)	14 (6.8)	0.273
Biliary metal stent	20 (9.5)	19 (9.3)	0.902
Pancreatic stent (prophylactic)	4 (1.9)	5 (2.4)	0.791
Pancreatic stent (therapeutic)	2 (0.9)	3 (1.4)	0.084
Endoscopic nasobiliary drainage	19 (9)	14 (6.8)	0.273
Trainee involvement	46 (22)	43 (21.1)	0.683
CBD diameter (mean ± SD) (mm)	11.3 ± 5.8	11.1 ± 5.4	0.983
Diverticulum	45 (21.5)	40 (19.7)	0.311
Cytology	28 (13.4)	27 (13.3)	0.872
Intrabiliary biopsy	2 (0.9)	3 (1.4)	0.084
Pancreatic duct-tissue sampling	0 (0)	0 (0)	
Papilla Vateri biopsy	9 (4.3)	7 (3.4)	0.158
Final diagnosis after ERCP			
Coledocolitiasis	127 (60.7)	122 (60.3)	0.984
Benign biliary stricture	15 (7.1)	17 (8.3)	0.583
Indeterminate biliary stricture	5 (2.3)	7 (3.4)	0.571
Pancreatic head cancer	17 (8.1)	16 (7.8)	0.749
Cholangiocarcinoma	12 (5.7)	12 (5.9)	0.912
Bile leak	10 (4.7)	9 (4.4)	0.528
SOD (types I/II)	7 (3.3)	7 (3.4)	0.987
Papillary mass	7 (3.3)	6 (2.9)	0.837
Chronic pancreatitis	4 (1.9)	3 (1.4)	0.589
Other‡	5 (2.3)	4 (1.9)	0.760
Overall success	206 (98.5)	199 (98)	0.996
Postamylase level (4 h) [median (minimum-maximum)] (IU/L)	79 (21-879)	125 (29-9625)	0.018
Postamylase level (24 h) (IU/L)	77 (12-455)	158 (33-1397)	0.011

*Difficult cannulation was defined according to the European Society of Gastrointestinal Endoscopy (ESGE) Guideline[23]: > 5 contacts with the papilla or > 5 minutes of cannulation attempts or > 1 unintended pancreatic duct cannulation, or those with failed cannulation to the target duct.

†Wire-guided cannulation method was used in all cases which is used routinely and contrast-assisted cannulation is never used principally in our clinic.

‡Other: portal biliopathy (n = 1), Mirizzi syndrome (n = 2), primary sclerosing cholangitis (n = 1), choledochal cyst (n = 1), hepatic lymph node metastasis (n = 1), gallbladder cancer (n = 2), hepatocellular carcinoma (n = 1).

CBD indicates common bile duct; EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction, the diagnosis of which was made according to the criteria of Rome 4.

(60.5%). The overall success rate of selective cannulation was 98.5%, and there was no significant difference between the 2 groups. There was also no statistically significant difference between the groups in terms of indications, the time to selective cannulation, and the mean procedure time for ERCP (Table 2).

In all, patients (7 in each group) underwent ERCP for sphincter of Oddi dysfunction types I and II for empiric sphincterotomy without manometry. In this study, because WGC was performed in all patients in both groups, no patients underwent pancreatic injection and acinarization.

Primary Outcome

The incidence rates of patient-related and procedure-related risk factors for pancreatitis were similar in both groups. The primary outcome of PEP occurred in 16 of 412 patients (3.8%); 1 (0.4%) PEP developed in the epinephrine group, and 15 PEPs were documented in the 203 (5.1%) patients in the indomethacin group ($P < 0.001$) (Fig. 3, Table 3). Of the latter, 13 cases were mild and 2 were moderate. Severe pancreatitis did not develop in any patient in either group (Table 3). The patients with PEP were conservatively managed. None of them required surgical, endoscopic, or interventional radiologic treatment, and all of them recovered uneventfully. In this study, pancreatic duct stenting was performed in 9 (2.1%) cases; 4 (1.9%) in the epinephrine group and 5 (2.4%) in the indomethacin group; none of these patients developed PEP.

Upon univariate logistic regression analyses, females under the age of 35 years [odds ratio (OR) = 0.346; 95% confidence interval (CI): 0.107-1.114; $P = 0.075$], suspected sphincter of Oddi dysfunction (type I/II) (OR = 0.210; 95% CI: 0.055-0.800; $P = 0.022$), precut sphincterotomy (OR = 0.116; 95% CI: 0.022-0.622; $P = 0.012$), and epinephrine injection (OR = 14.521; 95% CI: 1.882-112.06; $P = 0.010$) were significantly associated with PEP. Multivariate analyses showed that only epinephrine injection (OR = 3.740; 95% CI: 1.177-11.878; $P = 0.025$) was significantly associated with PEP. Univariate and multivariate logistic regression analyses along with the dependent variables are shown in Table 4.

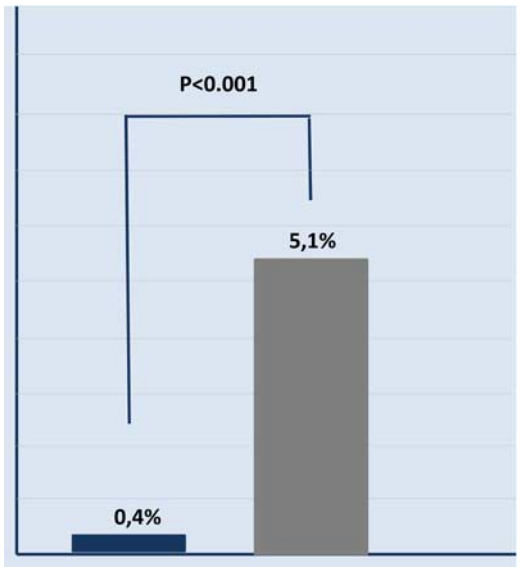

FIGURE 3. Incidence of post–endoscopic retrograde cholangiopancreatography pancreatitis. full color online

TABLE 3. Incidence of Hyperamylasemia and Post–Endoscopic Retrograde Cholangiopancreatography Pancreatitis

	n (%)		
	Epinephrine and Indomethacin Group (N = 209)	Indomethacin Group (N = 203)	*P*
Overall			
Hyperamylasemia, 4 h	19 (9.0)	49 (24.1)	< 0.001
Hyperamylasemia, 24 h	16 (7.6)	50 (24.6)	< 0.001
Pancreatitis	1 (0.4)	15 (5.1)	< 0.001
Mild/moderate/severe (n)	1/0/0	13/2/0	
Death	0 (0)	0 (0)	
High-risk states	69 (33)	49 (24.1)	
Hyperamylasemia, 4 h	8 (11.5)	18 (36.7)	< 0.001
Hyperamylasemia, 24 h	7 (10.1)	19 (38.7)	< 0.001
Pancreatitis	1 (0.4)	5 (9.8)	< 0.001
Mild/moderate/severe (n)	1/0/0	4/1/0	
Death	0 (0)	0 (0)	
Average-risk states	140 (66)	154 (75.8)	
Hyperamylasemia, 4 h	3 (1.4)	33 (16.2)	< 0.001
Hyperamylasemia, 24 h	5 (2.3)	10 (4.9)	< 0.001
Pancreatitis	0 (0)	10 (4.9)	< 0.001
Mild/moderate/severe (n)		9/1/0	
Death	0 (0)	0 (0)	

Secondary Outcomes

Post-ERCP hyperamylasemia occurred in 66 of 412 patients (16%): 16 of 209 patients (7.6%) in the epinephrine group and 50 of 203 (24.6%) in the indomethacin group. This difference was significant ($P < 0.001$) (Fig. 4, Table 3).

Other Adverse Events

During the study, 5 (1.2%) cases developed post-sphincterotomy bleeding, all of which were in the indomethacin group (2.4%; $P < 0.001$). None of the bleeding events resulted in the transfusion of > 2 U of packed red blood cells or surgical, endoscopic, or interventional radiologic treatment. Periampullary retroperitoneal perforation (Stapfer type II) occurred in 4 patients (2 in each group), and both

TABLE 4. Univariate and Multivariate Analyses of Risk Factors for Post–Endoscopic Retrograde Cholangiopancreatography Pancreatitis

Factors	*P*	Odds Ratio	95% CI
Univariate analysis			
Patient-related			
Female, age ≤ 35 y	0.075	0.346	0.107-1.114
Female	0.316	1.722	0.595-4.981
Suspected SOD (types I/II)	0.022	0.210	0.055-0.800
Epinephrine injection	0.010	14.521	1.882-112.06
Procedure-related			
Difficult cannulation	0.900	1.087	0.297-3.979
Needle-knife fistulotomy	0.997	1.125	0.167-4.252
Precut sphincterotomy	0.012	0.116	0.022-0.622
Multivariate analysis			
Epinephrine injection	0.025	3.740	1.177-11.878

CI indicates confidence interval; SOD, sphincter of Oddi dysfunction.

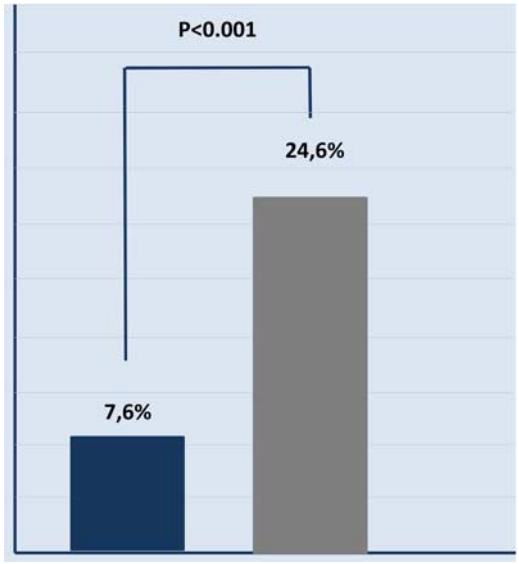

FIGURE 4. Incidence of post–endoscopic retrograde cholangiopancreatography hyperamylasemia. full color online

patients recovered uneventfully after treatment with fully covered, self-expandable metallic stents. The incidence rates of cholangitis and cholecystitis were not significantly different between the 2 groups. In addition, there were no adverse effects, including arrhythmias, acute coronary events, strokes, or hypertension, associated with epinephrine injection (Table 5).

DISCUSSION

Our results showed that when a submucosal epinephrine injection around the papilla of Vater was added to rectal indomethacin, the incidence of PEP was significantly reduced. The rate of hyperamylasemia, which may be a harbinger of PEP, was also significantly lower in the epinephrine group than it was in the indomethacin group.

TABLE 5. Incidence of Other Adverse Events

	n (%)		
	Epinephrine and Indomethacin Group (N = 209)	Indomethacin Group (N = 203)	*P*
Adverse events			
Bleeding	0 (0)	5 (2.4)	< 0.001
Mild/moderate/severe (n)	0/0/0	5/0/0	
Perforation	2 (0.9)	2 (0.9)	1.000
Mild/moderate/severe	1/1/0	1/1/0	
Cholangitis	5 (2.3)	5 (2.4)	0.828
Mild/moderate/severe	3/2/0	3/1/1	
Cholecystitis	4 (1.9)	5 (2.4)	0.316
Cardiopulmonary events	2 (0.9)	2 (0.9)	1.000
Arrhythmia	1 (0.4)	1 (0.4)	1.000
Death	0 (0)	0 (0)	

After the publication of Japanese studies that used an epinephrine spray, Akshintala et al's[4] NMA reported that topical epinephrine sprayed on the papilla of Vater was the most effective drug in preventing PEP, followed by rectal NSAIDs. However, Kamal et al[24] showed in their RCT that the epinephrine spray did not reduce the incidence of PEP, and they suggested that epinephrine should have been applied using a different method than spraying it onto the papilla, such as in the form of subcutaneous injection. Unlike mucosal spraying, subcutaneous injection of epinephrine has a significantly longer duration of action; the injection lasts for at least 120 minutes, while mucosal sprays only work for 1 to 5 minutes.[18,19]

Although it was not the primary purpose, we found that the method used in this study was highly effective at reducing postsphincterotomy bleeding. No bleeding developed in the epinephrine group, but 2.3% of the indomethacin group developed bleeding following the procedure.

We chose a concentration of 1:1000 epinephrine to avoid inflating too much of the papilla orifice by instilling a large amount of saline. Using high concentrations of epinephrine may cause concern for some vasopressor adverse effects; however, according to Menninger and colleagues,[25,26] high doses of epinephrine administered to all locations of the gastrointestinal lumen except the esophagus were found to have no significant systemic vasopressor effects. In our study, there were no adverse effects, including arrhythmias, acute coronary events, stroke, or hypertension, that could be attributed to epinephrine.

Although the concentration seems high, the total amount of epinephrine used in our study was the same amount that is frequently used in daily clinical procedures, such as polypectomy, gastrointestinal bleeding, endoscopic submucosal dissection, etc. Epinephrine injection is generally the most preferred treatment method for postsphincterotomy bleeding; no adverse events attributed to peripapillar epinephrine injection have been reported to date.[27,28]

Our study was the first report to determine if epinephrine injection can prevent papillary edema and the resulting pancreatic damage associated with ERCP; however, this study had some limitations. First, this study was carried out retrospectively, and it is well known that all manipulations, maneuvers, and critical but important details that occur during the ERCP procedure are often not noted as meticulously and exactly in the final report. The second limitation was our relatively small sample size. Because of these limitations, further investigations are warranted for prospective RCTs to confirm the efficacy of epinephrine injections in preventing PEP.

In conclusion, addition of submucosal epinephrine injection to rectal indomethacin administration significantly reduced the incidence of PEP, post-ERCP hyperamylasemia, and postsphincterotomy bleeding.

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