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CLINICAL—PANCREAS

Rectal Indomethacin Reduces Pancreatitis in High- and Low-Risk Patients Undergoing Endoscopic Retrograde Cholangiopancreatography

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BACKGROUND & AIMS: Rectal indomethacin reduces the risk of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). Most studies of its efficacy included high-risk cohorts and excluded low-risk patients, including those with malignant biliary obstruction. We investigated the potential of rectal indomethacin to prevent post-ERCP pancreatitis (PEP) in a variety of patients. **METHODS:** We performed a retrospective cohort study of 4017 patients who underwent ERCP at the Hospital of the University of Pennsylvania, from 2009 and 2015, including 823 patients with malignant biliary obstruction. After June 2012, with a few exceptions, patients received indomethacin after their procedure. We collected data from patients' records on demographic and clinical features, procedures, and development of PEP. PEP was defined by consensus criteria. Multivariable logistic regression was used to determine adjusted odds ratios (ORs) for the association between indomethacin and PEP. **RESULTS:** Rectal indomethacin reduced the odds of PEP by 65% (OR, 0.35; 95% confidence interval [CI], 0.24–0.51; $P < .001$) and moderate-to-severe PEP by 83% (OR, 0.17; 95% CI, 0.09–0.32; $P < .001$). In patients with malignant obstruction, rectal indomethacin reduced the risk of PEP by 64% (OR, 0.36; 95% CI, 0.17–0.75; $P < .001$) and moderate-to-severe PEP by 80% (OR, 0.20; 95% CI, 0.07–0.63; $P < .001$). Among patients with malignant obstruction, rectal indomethacin provided the greatest benefit to patients with pancreatic adenocarcinoma: 2.31% of these patients who received rectal indomethacin developed PEP vs 7.53% who did not receive rectal indomethacin ($P < .001$) and 0.59% of these patients who received rectal indomethacin developed moderate-to-severe PEP vs 4.32% who did not receive rectal indomethacin ($P = .001$). **CONCLUSIONS:** In a large retrospective cohort study of patients undergoing ERCP that included low-risk patients and patients with malignant biliary obstruction, rectal indomethacin was associated with a significant decrease in the absolute rate and severity of pancreatitis.

Keywords: Biliary Tree; Pancreas; Inflammation; Prevention.

Endoscopic retrograde cholangiopancreatography (ERCP) is a common diagnostic and therapeutic procedure for disorders of the biliary tree and pancreas. The most common adverse event after this procedure is post-ERCP pancreatitis (PEP), occurring in 2%–9% of patients in most studies.[1–5] It can be a severe complication leading to substantial morbidity and health care expenditures of, on average, $200 million annually in the United States.[4,6,7]

Several patient-related risk factors have been identified for PEP, including young age, female sex, normal serum bilirubin, prior PEP and, of particular significance, sphincter of Oddi dysfunction (SOD), which is associated with up to a 15%–20% increase in the risk of PEP and an increased risk of severe pancreatitis.[2,3,5,8–10] Studies have found that these different risk factors have a synergistic effect.[3,10] Procedure-related risk factors for PEP include traumatic and repeated cannulation, pancreatic sphincterotomy, precut sphincterotomy, balloon dilation of an intact biliary sphincter, and endoscopic papillectomy.[8,10–12] On the other hand, factors traditionally believed to be protective against PEP include chronic pancreatitis, older age, and malignant obstruction, particularly due to pancreatic adenocarcinoma.[3] Malignant obstruction of the pancreatic duct is believed to cause significant ductal and parenchymal atrophy and damage, which decreases pancreatic enzyme production.[13] Studies have shown that the PEP rate in such patients varies from 0.1% to 2.4%.[13–15]

Several approaches to reduce the risk of PEP have been studied. Insertion of pancreatic duct (PD) stents has been shown to reduce the risk of PEP in high-risk patients

Abbreviations used in this paper: **CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; NNT, number needed to treat; NSAID, nonsteroidal anti-inflammatory drug; OLT, orthotropic liver transplantation; OR, odds ratio; PD, pancreatic duct; PEP, post-ERCP pancreatitis; RCT, randomized controlled trial; SOD, sphincter of Oddi dysfunction.**

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and the risk of severe PEP.[16–18] However, stent placement may have drawbacks, which include failed placement, migration, and ductal perforation.[17,19–21] Therefore, use of PD stents is limited to patients with an increased risk of moderate-to-severe pancreatitis. Additionally, a significant proportion of endoscopists decide not to place PD stents due to a lack of experience.[22]

Beyond procedural considerations and endoscopic intervention, different pharmacologic agents have been studied to prevent PEP. Of these, nonsteroidal anti-inflammatory drugs (NSAIDs) administered rectally have shown potential benefit, despite conflicting findings in multiple single-center randomized controlled trials (RCTs). Elmunzer et al[6] performed a multicenter RCT comparing a single dose of 100 mg rectal indomethacin with placebo after ERCP in selected high-risk patients and found that 9.2% of patients in the indomethacin group developed PEP compared with 16.9% in the placebo group, a statistically significant difference. The incidence of moderate-to-severe pancreatitis was also significantly decreased in the indomethacin group compared with placebo. However, the majority of patients in this study had possible SOD, thus limiting the generalizability of the findings. In such patients, the benefit of ERCP is unclear and there is an elevated risk of PEP.[23] Additionally, the majority of patients also had a PD stent attempted or placed and, as a result, it was unclear whether indomethacin was the sole contributor to improved outcomes. Finally, the authors specifically excluded patients with malignant biliary obstruction and patients with other common low-risk indications for ERCP. In a subsequent meta-analysis of 7 RCTs with a total of 2133 patients, rectal indomethacin demonstrated a similar reduction in PEP.[24] However, the majority of patients were high risk and all studies included patients with suspected SOD.[24] A recent RCT involving mainly average-risk patients failed to find a benefit with rectal indomethacin administration when compared with placebo.[25] Therefore, the benefit of rectal NSAIDs has not been definitively demonstrated in low-risk patients and patients with malignant obstruction, who together comprise the majority of patients undergoing ERCP in real-world practice.[26]

In this retrospective cohort study, we examined the effect of rectal indomethacin on the rates and severity of PEP in a large real-world cohort, which included patients traditionally considered low risk for PEP.

Methods

We conducted a retrospective cohort study at the Hospital of the University of Pennsylvania. Between January 1, 2009 and December 1, 2015, a total of 4163 patients underwent ERCP at the inpatient or outpatient endoscopy units at the Hospital of the University of Pennsylvania and 4017 were eligible for study inclusion. One hundred and forty-six patients whose procedures were terminated before reaching the major papilla due to luminal obstruction or patient intolerance were not eligible for study inclusion. Advanced endoscopy fellows were involved in performing ERCPs, but second- and third-year gastroenterology fellow were not involved during the study period. From January 1, 2009 to June 1, 2012, patients did not receive indomethacin. After June 1, 2012, rectal indomethacin was routinely considered after the procedure unless the patient had a contraindication, such as acute kidney injury or active peptic ulcer disease. The indomethacin group consisted of patients who received 100 mg rectal indomethacin immediately upon withdrawal of the duodenoscope, while the unexposed group consisted of patients who did not receive rectal indomethacin. The study was approved by the institutional review board at our institution.

The primary outcome was the development of PEP as defined by consensus criteria, including the presence of abdominal pain consistent with pancreatitis, coupled with a need for an unplanned hospital stay or an extension of a planned hospital stay by at least 2 days and a serum amylase at least 3 times above the upper limit of normal 24 hours after the procedure.[16] The secondary outcome was the severity of PEP categorized as mild (2–3 days of hospitalization), moderate (4–10 days of hospitalization), or severe (10 days of hospitalization, development of necrosis or pseudocyst requiring drainage) in accordance with consensus criteria.[16]

Patients were observed in the recovery area for at least 90 minutes after the procedure and assessed by the endoscopy nurse and endoscopist before departure. If the patient had symptoms concerning for acute pancreatitis, the patient was admitted to the hospital from the outpatient setting or, if inpatient, was kept in the hospital for monitoring. If the patient was believed to have symptoms consistent with PEP, an amylase and/or lipase were checked within the first 24 hours of hospitalization. Patients who were discharged after their ERCP without concerning symptoms were contacted by telephone 24–72 hours after the procedure to detect delayed presentation of PEP. Any patient responses that were of concern were forwarded to the endoscopist and clinical staff, who triaged them by routinely recommending emergency department evaluation and/or hospitalization. For patients who were inpatients, the responsible inpatient team and the gastrointestinal consult service would follow-up within 24 hours to capture delayed presentations of PEP. These patients' charts, consult notes, and discharge summaries were reviewed to detect presentations of PEP. Patients who developed PEP were treated with standardized guideline-based management for acute pancreatitis overseen by the treating physician.[27] Patients who developed PEP continued to have follow-up during their hospitalization with their treating physician, as well as a 30-day follow-up.

Statistical Analysis

Patient data including demographic and procedural characteristics; medications provided before, during, and after the procedure; type of sedation received, as well as immediate and delayed adverse events, were collected. Differences in demographic and/or clinicopathologic variables between the exposed (rectal indomethacin) and unexposed groups were analyzed using the χ^2 and Fisher's exact tests for categorical variables and Student t test and Wilcoxon rank sum tests for continuous variables.

Patients who received rectal indomethacin were compared with those who did not receive indomethacin after their ERCP. An analysis of clinical and procedural factors associated with PEP was then conducted by performing univariable logistic regression analyses with development of PEP as the dependent variable and the following independent variables: age, sex, inpatient status, procedure indication, glucagon usage,

antibiotic usage, total bilirubin, prior pancreatitis, prior PEP, pancreatic sphincterotomy, precut sphincterotomy, number of cannulation attempts, ampullectomy, pancreatic brush cytology, biliary sphincterotomy, bile duct stent placement, trainee involvement, balloon dilatation, balloon sphincteroplasty, pancreatic acinarization, endotracheal intubation, type of anesthesia received, and year of the procedure. Any variable associated with indomethacin administration and with PEP ($P < .15$) in the univariable analysis was included in a multivariable logistic regression model, with PEP as the dependent variable. Performance of biliary sphincterotomy and PD cannulation attempts were found to be potential confounders in our cohort and were included in the final logistic regression model. A separate multivariable logistic regression model with classic PEP risk factors was also developed and included age, sex, total bilirubin, recurrent pancreatitis, prior PEP, precut sphincterotomy, PD placement, and number of injections in the PD. The 2 models were compared with no significant differences seen. A similar process was used to build a multivariable logistic regression model, with severity of pancreatitis (percent of patients with moderate-to-severe PEP) as the dependent variable. Additionally, given that rates of PEP differ based on risk and etiology of biliary obstruction, a subgroup analysis to examine the effect of indomethacin in the setting of malignant biliary obstruction was proposed a priori and performed.

Another secondary propensity-score matched analysis was performed comparing the indomethacin and unexposed groups. Propensity scores were generated using covariates associated with indomethacin administration, including patient- and procedure-specific characteristics. The logistic regression model utilized to derive the propensity score included the following 22 variables: age, sex, inpatient status, procedure indication, glucagon usage, antibiotic usage, total bilirubin, prior pancreatitis, prior PEP, pancreatic sphincterotomy, precut sphincterotomy, number of cannulation attempts, ampullectomy, pancreatic brush cytology, biliary sphincterotomy, bile duct stent placement, trainee involvement, balloon dilatation, balloon sphincteroplasty, pancreatic acinarization, endotracheal intubation, and type of anesthesia received. Using a caliper of 0.01, one-to-one matching was employed based on the propensity score. Based on these criteria, a total of 3268 patients, 1634 indomethacin-exposed and 1634 unexposed, were included in the propensity score matched analysis (see Supplementary Material, "Propensity-Matched Analysis"). All statistical analyses were performed with MATLAB (Mathworks, Natick, MA) and STATA 14 statistical package (StataCorp LP, College Station, TX). A P value $<.05$ was considered statistically significant for all analyses.

Based on an estimated overall PEP rate of 5% at our institution, we estimated that having 960 patients in each cohort and 1920 patients total would power our study to detect a 50% reduction in the incidence of PEP from 5% in the unexposed group to 2.5% in the indomethacin group, with an α of .05 and power of .90. Using our final sample size of 3942 patients, we had a 98.5% power to detect a 50% reduction in the odds of developing PEP.

Results

A total of 4017 patients were included in the analysis, with 2007 patients in the indomethacin cohort and 2010 patients in the cohort that did not receive indomethacin. No patients received indomethacin before June 2012; 257 patients after June 2012 did not receive indomethacin and were part of the unexposed cohort. Baseline characteristics were compared between the 2 cohorts with significant differences being shown in rates of PD stent placement, anesthesia technique, and PD cannulation (Table 1). The significant differences in anesthesia technique between the indomethacin-exposed and unexposed groups were mainly due to introduction of anesthesia providers in the outpatient setting. Furthermore, anesthesia technique was not found to be a confounder in the multivariable regression analysis. PEP occurred in 1.99% (40 of 2007) of patients in the indomethacin group compared with 4.73% (95 of 2010) of patients in the unexposed group (Figure 1). Two patients in the unexposed group died after developing pancreatitis, while no patients in the indomethacin group died after developing pancreatitis ($P = .5$). The rate of PEP was lower in individuals who received indomethacin compared with unexposed patients in both patients with a native papilla (2.92% [39 of 1195] vs 7.48% [72 of 962]; $P < .001$) and patients who were post-sphincterotomy (0.62% [5 of 812] vs 2.19% [23 of 1048]; $P = .004$). Three patients (2 in the indomethacin and 1 in the unexposed group) underwent ERCP for suspected SOD type I for empiric sphincterotomy without manometry.

We explored individual patient and procedural variables, including PD stent placement, PD cannulation, anesthesia technique, and year the ERCP was performed, and found only PD cannulation and biliary sphincterotomy to be potential confounders. A logistic regression model adjusting for PD cannulation and biliary sphincterotomy showed that rectal indomethacin had an adjusted OR of 0.35 (95% CI, 0.24–0.51; $P < .001$) for PEP (Figure 2). When adjusting for classic PEP risk factors, use of indomethacin had a similar OR of 0.38 (95% CI, 0.26–0.56; $P < .001$) for PEP. A separate model analyzing patients who underwent ERCP after June 2012, adjusting for PD cannulation and biliary sphincterotomy, demonstrated that rectal indomethacin had an adjusted OR of 0.14 (95% CI, 0.06–0.30; $P < .001$) for PEP, thereby confirming the results from the primary analysis (see Supplementary Material, "Additional Potential Confounders"). With the secondary propensity-score matched analysis, indomethacin had an adjusted OR of 0.35 (95% CI, 0.23–0.52; $P < .001$) and an OR of 0.42 (95% CI, 0.22–0.84; $P < .001$) when adjusted for the year of the procedure, thereby confirming the findings from the primary model (see Supplementary Material, "Propensity-Matched Analysis"). The number needed to treat (NNT) for indomethacin was 34 patients to prevent 1 case of PEP.

For the secondary outcome, 0.55% (11 of 2007) of the indomethacin group developed moderate-to-severe PEP compared with 2.68 % (54 of 2010) of the unexposed group. Patients with a native papilla had rates of moderate-to-severe PEP of 0.84% (10 of 1195) and 4.47% (43 of 962) for the indomethacin-exposed and unexposed groups, respectively ($P < .001$). Patients who were post-sphincterotomy had PEP rates of 0.12% (1 of 812) and 1.05% (11 of 1048) for the indomethacin and unexposed groups, respectively ($P = .01$). A logistic regression model

Table 1. Baseline Characteristics of Patients Who Received Indomethacin Compared With Unexposed Patients

	Indomethacin group (N = 2007)	No indomethacin group (N = 2010)	*P* value
Patient characteristics			
Average age, (*y*)	58.5 ± 17.1	58.6 ± 15.4	.44
Gender, % *male*	1119 (55.7)	1123 (55.8)	.60
Inpatient	859 (42.8)	753 (37.5)	.25
Glucagon usage	16 (0.8)	17 (0.8)	.54
Antibiotic usage	435 (21.7)	475 (23.6)	.43
Average bilirubin, (*mg/dL*)	4.0 ± 5.2	3.6 ± 4.8	.19
History of pancreatitis	131 (6.5)	128 (6.4)	.33
History of post-ERCP pancreatitis	46 (2.3)	51 (2.5)	.41
Indication			.63
OLT	279 (14)	468 (23)	
Gallstone	532 (27)	468 (23)	
Malignancy	396 (20)	427 (21)	
Bile leak	169 (8)	127 (6)	
PSC	91 (5)	90 (4)	
Benign pancreatic	123 (6)	94 (5)	
Benign biliary	280 (14)	222 (11)	
Procedural characteristics			
Pancreatic sphincterotomy	60 (3.0)	46 (2.3)	.07
Precut sphincterotomy	153 (7.6)	179 (8.9)	.14
Performance of ampullectomy	26 (1.3)	21 (1.0)	.24
PD cannulated	416 (20.7)	357 (17.8)	**.002**
PD injected	299 (14.9)	286 (14.2)	.10
Acinarization	99 (4.9)	84 (4.2)	.08
Pancreatic duct brushing	13 (0.6)	14 (0.6)	.54
Biliary sphincterotomy	1144 (57.0)	1092 (54.3)	.47
PD placement	101 (5.0)	77 (3.8)	**.02**
Trainee involvement	1742 (86.8)	1823 (90.6)	.14
Stent placement	1047 (52.1)	1107 (55.0)	.71
CBD brushing	406 (20.2)	415 (20.6)	.80
Endotracheal intubation	350 (17.4)	39 (1.9)	**<.001**
Sedation by anesthesia provider	1998 (99.6)	1868 (92.9)	**<.001**
Dilatation performed	349 (17.4)	406 (20.2)	.06

NOTE. Statistically significant differences between the 2 groups are in *bold* type. Data is given as n(%) unless otherwise noted. CBD, common bile duct; PSC, primary sclerosing cholangitis.

adjusting for PD cannulation and biliary sphincterotomy showed that rectal indomethacin had an adjusted OR for developing moderate-to-severe PEP of 0.17 (95% CI, 0.09–0.32; $P < .001$). Another model adjusting for classic PEP risk factors showed a similar OR of 0.19 (95% CI, 0.10–0.36; $P < .001$). The NNT for preventing 1 case of moderate-to-severe PEP was 45.

Patients With Malignant Obstruction

Eight hundred and twenty-three patients included in this analysis had malignant biliary obstruction due to pancreatic adenocarcinoma, cholangiocarcinoma, ampullary carcinoma, or metastasis to the pancreaticobiliary region. Three hundred and ninety-six patients received rectal indomethacin and 427 did not. Background characteristics were compared between the indomethacin and unexposed cohorts, with significant differences seen in pancreatic sphincterotomy, PD cannulation, and anesthesia technique, but only PD cannulation and biliary sphincterotomy were found to be potential confounders and required adjustment in the logistic regression model (Table 2). PEP occurred in 2.78% (11 of 396) of patients in the indomethacin group compared with 5.87% (25 of 427) of unexposed patients ($P < .001$). Similarly, patients with a native papilla who received indomethacin had a lower rate of PEP compared with unexposed patients (5.31% vs 12.30%; $P = .01$). When stratified by type of malignancy, patients with pancreatic adenocarcinoma had significantly lower rates of PEP with indomethacin compared with those who did not receive indomethacin (2.31 % vs 7.53%; $P = .001$) (Figure 3). A significant difference was not observed in patients with cholangiocarcinoma or other malignancies. A logistic regression model adjusting for PD cannulation and biliary sphincterotomy showed that rectal indomethacin had an adjusted OR of 0.36 (95% CI, 0.17–0.75; $P < .001$) (Figure 4) for PEP in patients with malignancies. The model rerun adjusted for classic PEP risk factors showed a similar OR of 0.38 (95% CI, 0.18–081; $P = .004$) for PEP. The NNT for preventing 1 case of PEP in patients with malignant biliary obstruction for indomethacin was 23.

For the secondary outcome, 1.01% (4 of 396) of the indomethacin group developed moderate-to-severe PEP compared with 3.52% (15 of 427) of the unexposed group with malignant obstruction ($P = .01$). Patients with a native

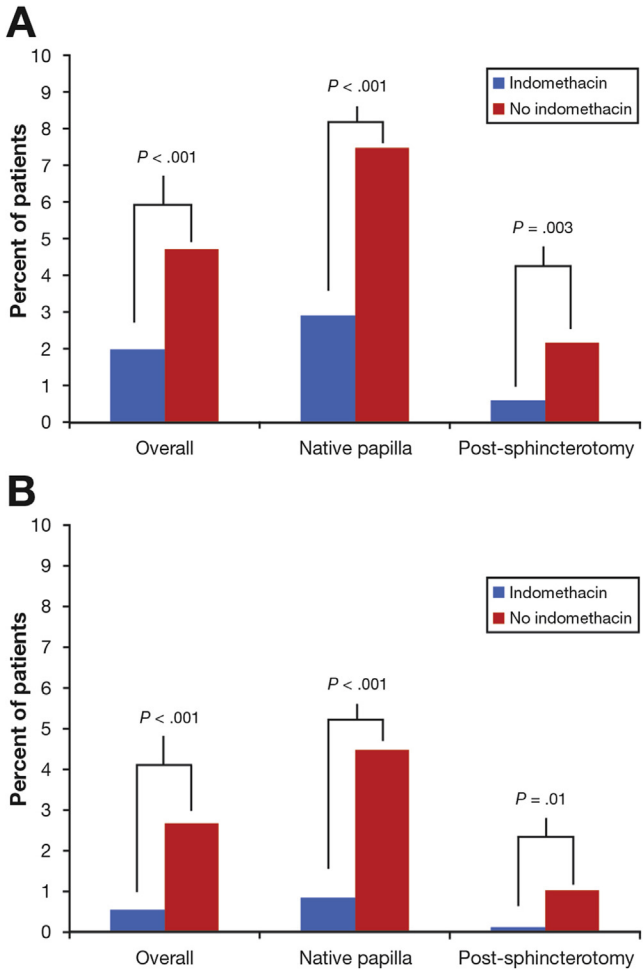

Figure 1. (*A*) Chart comparing the percentage of patients with PEP in the indomethacin and unexposed groups overall, in patients with native papilla, and in patients who are post-sphincterotomy. (*B*) Chart comparing the percentage of patients who developed moderate-to-severe pancreatitis in the indomethacin and unexposed groups overall, in patients with native papilla and in patients who are post-sphincterotomy.

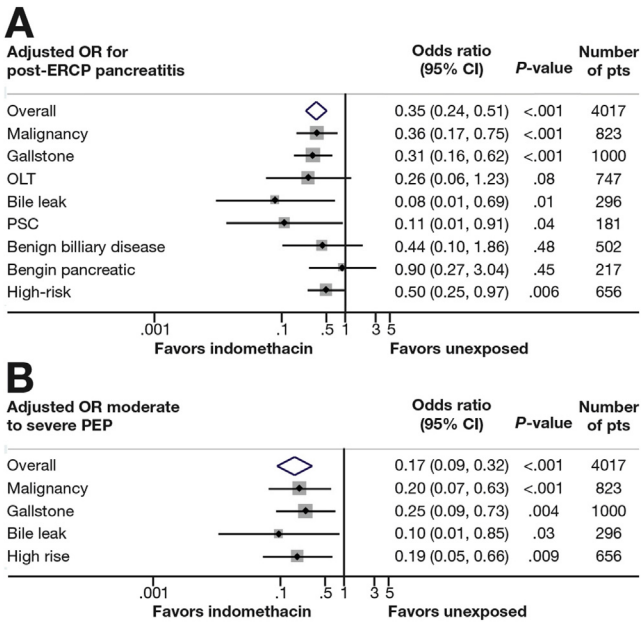

Figure 2. (*A*) A Forest plot displaying the OR of developing PEP comparing indomethacin with the unexposed group overall and in various subgroups. (*B*) A Forest plot displaying the OR of developing moderate-to-severe pancreatitis comparing indomethacin with the unexposed group overall and in various subgroups. In subgroups where there were no events or episodes of PEP, the OR was not pictured.

papilla and malignant obstruction had rates of moderate-to-severe PEP of 1.93% (4 of 207) and 6.95% (13 of 187) for the indomethacin and unexposed groups, respectively ($P = .01$). Similar to the primary outcome, pancreatic adenocarcinoma patients garnered the majority of the benefit in reduction of moderate-to-severe pancreatitis (0.59% vs 4.32%; $P = .001$). The adjusted OR for developing moderate-to-severe pancreatitis with rectal indomethacin in patients with malignant obstruction was 0.20 (95% CI, 0.07–0.63; $P < .001$). Another model adjusting for classic PEP risk factors showed a similar OR of 0.25 (95% CI, 0.08–0.75; $P = .001$). The NNT for preventing 1 case of moderate-to-severe PEP in patients with malignant biliary obstruction for indomethacin was 35.

Post-Orthotropic Liver Transplantation Patients

Two hundred and seventy-nine patients in the indomethacin group and 468 patients in the unexposed group were post-orthotropic liver transplantation. Among these patients, 0.71% of the indomethacin group developed PEP compared with 2.14% in the unexposed group ($P = .11$). In post-OLT patients with a native papilla, PEP rates were 0.58% and 3.88% in the indomethacin and unexposed groups, respectively ($P = .02$). Similarly, rate of moderate-to-severe PEP in post-OLT patients was 0% in the indomethacin group compared with 1.28% in the unexposed group ($P = .05$). Additionally, rate of moderate-to-severe PEP in post-OLT patients with a native papilla was 0% in the indomethacin group compared with 1.94% in the unexposed group ($P = .08$).

Gallstone Disease

Five hundred and thirty-two patients in the indomethacin group and 468 patients in the unexposed group underwent ERCP for choledocholithiasis. PEP occurred in 2.44% of the indomethacin group compared with 5.98% in the unexposed group ($P < .001$). In patients with a native papilla, PEP occurred in 2.83% of the indomethacin group compared with 7.09% of the unexposed group ($P = .005$). Similarly, rates of moderate-to-severe PEP were 0.93% and 2.78% in the indomethacin and unexposed groups, respectively ($P = .02$). In patients with gallstone disease and a native papilla, rates of moderate-to-severe PEP were 0.94% and 3.97% in the indomethacin and unexposed groups, respectively ($P = .02$).

Bile Leak

PEP occurred in 0.60% of the 169 patients with bile leak compared with 4.72% of 127 such patients in the unexposed group ($P = .03$). Similarly, moderate-to-severe

Table 2. Baseline Characteristics of Patients With Malignant Biliary Obstruction Who Received Indomethacin Compared With Unexposed Patients

	Indomethacin group (N = 396)	No indomethacin group (N = 427)	*P* value
Patient characteristics			
Average age, (*y*)	65.5 ± 12.0	67.3 ± 11.1	.10
Gender, % *male*	215 (54.2)	255 (59.7)	.33
Inpatient	144 (36.4)	177 (41.5)	.82
Glucagon usage	2 (0.5)	7 (1.6)	.13
Antibiotic usage	147 (37.1)	137 (32.1)	.75
Average bilirubin, (*mg/dL*)	7.6 ± 6.5	7.0 ± 5.7	.19
History of pancreatitis	7 (1.8)	11 (2.6)	.34
History of post-ERCP pancreatitis	6 (1.5)	5 (1.2)	.84
Indication			.63
Pancreatic adenocarcinoma	173 (44)	186 (44)	
Cholangiocarcinoma	125 (32)	145 (34)	
Metastatic cancer	93 (23)	92 (22)	
Ampullary carcinoma	5 (1)	4 (1)	
Procedural characteristics			
Pancreatic sphincterotomy	9 (2.3)	2 (0.5)	**.02**
Precut sphincterotomy	36 (9.0)	40 (9.3)	.49
Performance of ampullectomy	1 (0.3)	0 (0.0)	.23
PD cannulated	59 (14.9)	41 (9.6)	**.005**
PD injection	42 (10.6)	40 (9.4)	.22
Acinarization	6 (1.5)	5 (1.2)	.41
Pancreatic duct brushing	6 (1.5)	2 (0.5)	.10
Biliary sphincterotomy	192 (48.4)	187 (43.7)	.88
PD placement	9 (2.3)	7 (1.6)	.30
Trainee involvement	365 (92.2)	406 (95.1)	.12
Stent placement	359 (90.7)	393 (92.0)	.22
CBD brushing	172 (43.4)	190 (44.5)	.45
Endotracheal intubation	60 (15.1)	13 (3.0)	**<.001**
Sedation by anesthesia provider	396 (100.0)	420 (98.3)	**.01**
Dilatation performed	42 (10.6)	36 (8.4)	.09

NOTE. Statistically significant differences between the 2 groups are in *bold* type. Data is given as n(%) unless otherwise noted. CBD, common bile duct.

PEP occurred in 0.60% and 3.93% of those cohorts ($P = 0.06$). In these patients with a native papilla, PEP occurred in 1.03% and 11.11% of the indomethacin and unexposed groups, respectively ($P = .005$), while moderate-to-severe PEP occurred in 1.05% and 9.26% of these groups ($P = .01$).

Primary Sclerosing Cholangitis

Of the 91 patients in the indomethacin group, 1.1% with primary sclerosing cholangitis developed PEP compared with 8.89% of the 90 patients in the unexposed group ($P = .01$). Moderate-to-severe pancreatitis occurred in 0% and 5.56% of these cohorts, respectively ($P = .01$). In patients with a native papilla, PEP occurred in 5.88% in both groups ($P = .74$), whereas in post-sphincterotomy patients, PEP occurred in 0% of indomethacin patients compared with 9.58% of unexposed groups ($P = .003$). In the post-sphincterotomy unexposed group, 5.47% developed moderate-to-severe PEP compared with 0 patients in the indomethacin group ($P = .02$).

Benign Pancreatic Disease

Of those undergoing ERCP for benign pancreatic disease, including PD strictures, PD leak, and PD stones, 123 patients received indomethacin and 94 did not receive the medication with similar rates of PEP observed between the 2 groups (5.69% vs 5.31%; $P = .45$). No significant differences were seen in the rate of PEP or severity in patients with native papilla or post-sphincterotomy.

Benign Biliary Disease

Benign biliary disease, including common bile duct and common hepatic duct strictures without malignancy and papillary stenosis, was the indication for ERCP in 280 patients in the indomethacin group and 222 patients in the unexposed group. PEP developed in 0.71% of the indomethacin cohort and 2.72% of the unexposed cohort PEP ($P = .08$); rates of moderate-to-severe PEP were 0% and 1.80%, respectively ($P = .02$). Among patients with a native papilla, 0% of the indomethacin group developed PEP compared with 5.10% of the unexposed group ($P = .004$). Moderate-to-severe PEP developed in 4.08% of the unexposed group with a native papilla compared with none in the indomethacin group ($P = .01$).

High-Risk Patients

Three hundred and thirty-one patients who received indomethacin and 336 unexposed patients met the

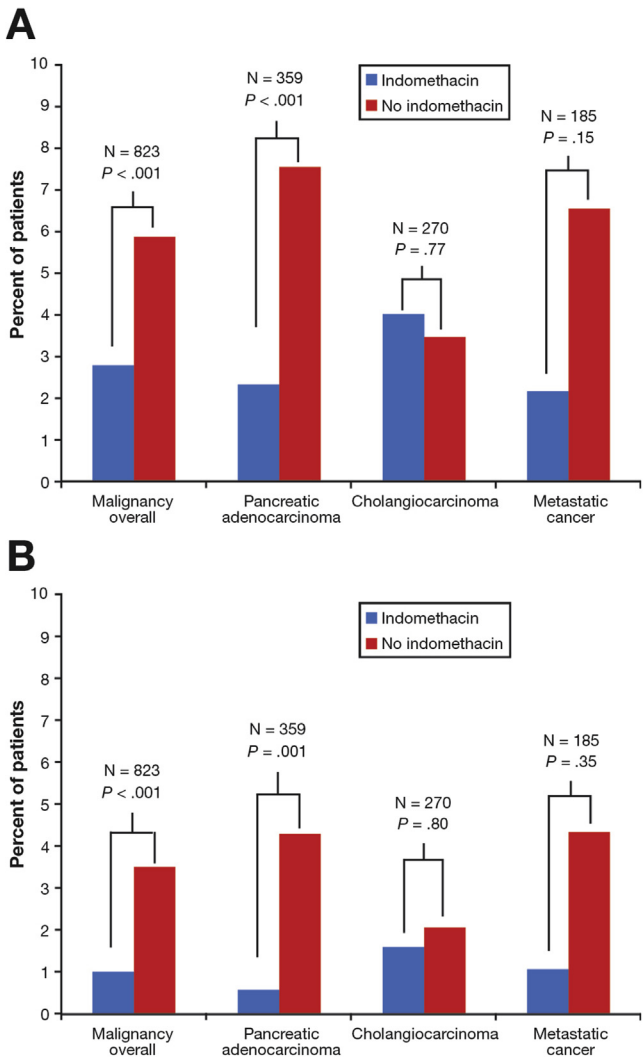

Figure 3. (*A*) Chart comparing the percentage of patients with malignant biliary obstruction who developed PEP in the indomethacin and unexposed groups overall, in patients with native papilla and in patients who are post-sphincterotomy. (*B*) Chart comparing the percentage of patients with malignant biliary obstruction who developed moderate-to-severe pancreatitis in the indomethacin and unexposed groups overall, in patients with native papilla and in patients who are post-sphincterotomy.

indications for high risk for PEP based on the criteria from Elmunzer et al[6] (see Supplementary Index). PEP developed in 4.5% of these patients in the indomethacin group compared with 8.03% of unexposed patients (P = .006). Furthermore, 0.9% of indomethacin patients developed moderate-to-severe PEP compared with 4.48% of the unexposed patients (P = .009). In these patients with a native papilla, 5.29% of the indomethacin group developed PEP compared with 9.03% of the unexposed group (P = .11) Moderate-to-severe PEP developed in patients with a native papilla 0.98% and 5.42% of the time for the indomethacin and unexposed groups, respectively (P = .008).

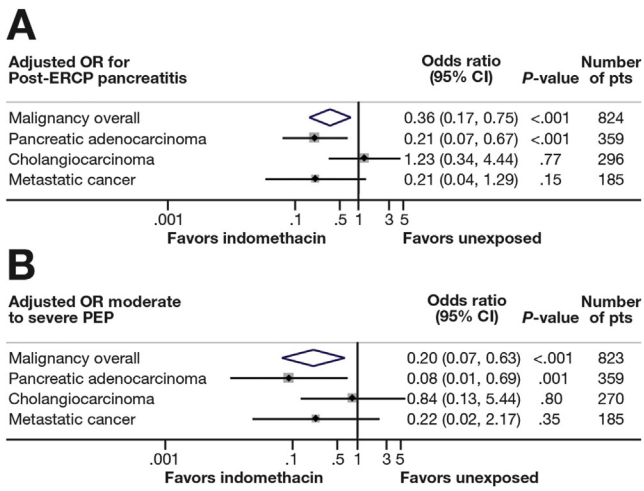

Figure 4. (*A*) A Forest plot displaying the OR of developing PEP in patients with malignant biliary obstruction comparing indomethacin with the unexposed group overall and in various subgroups. (*B*) A Forest plot displaying the OR of developed moderate-to-severe pancreatitis patients with malignant biliary obstruction comparing indomethacin with the unexposed group overall and in various subgroups. In subgroups, where there were no events or episodes of PEP, the OR was not pictured.

Adverse Events

Thirteen (0.65%) patients who received indomethacin developed post-procedural gastrointestinal bleeding compared with 9 (0.45%) patients who did not receive indomethacin (P = .52) (Table 3). All patients who developed post-procedural bleeding underwent sphincterotomy. No differences were seen in rates of perforation. No patients experienced an allergic reaction after indomethacin administration.

Discussion

Our findings show that post-procedural rectal indomethacin administration significantly reduced the incidence of PEP from 4.73% to 1.99% (P < .001). Furthermore, there was a significant decrease in the overall rate of moderate-to-severe PEP from 2.68% to 0.55% (P < .001) with the use of indomethacin. Among patients with malignant obstruction, there was a significant reduction in the rate of PEP (5.87% vs 2.78%; P < .001) and in the rate of moderate-to-severe PEP (3.52% to 1.01%; P < .001). Our study also demonstrated a significant reduction in PEP and moderate-to-severe PEP in other specific subgroups, which included patients with gallstones, bile leaks, and primary sclerosing cholangitis. Furthermore, a trend toward benefit with rectal indomethacin was seen in post-OLT patients. Our study confirmed a significant reduction in PEP rates and rate of moderate-to-severe PEP in high-risk patients.[19] In this subgroup, the magnitude of overall reduction was 8.03% to 4.50% (P = .04) for PEP and 4.48% to 0.90% (P = .003) for moderate-to-severe PEP, similar to estimates reported previously.[6]

Table 3. Adverse Events Associated With Endoscopic Retrograde Cholangiopancreatography in Both Indomethacin Group and Unexposed Group

Adverse event	Indomethacin group	Unexposed group	*P* value
Post-procedural bleeding	13 (0.65)	9 (0.45)	.52
Bleeding requiring ICU admission	6 (0.30)	8 (0.40)	.79
Perforation	2 (0.1)	1 (0.05)	.62

NOTE. Data given as n(%).
ICU, intensive care unit.

Prior studies have included both high- and low-risk patients, but they have not been powered to demonstrate a risk reduction in solely low-risk patients.[26] While investigators' primary aim was not to quantify this effect in low-risk patients, secondary analyses and subsequent meta-analyses were suggestive of benefit. Our study is unique in that it is the first large study to show a significant reduction in the rate of PEP in a primarily low-risk patient population. By contrast, the RCT conducted by Elmunzer et al[6] demonstrated effectiveness of rectal indomethacin in a high-risk group of patients, of whom 80% had concomitant PD stent placement and 80% had potential SOD dysfunction. Among patients without suspicion of SOD, their study did not show a statistically significant difference in outcomes. Even a subsequent meta-analysis showing benefit with indomethacin did not include trials with low-risk patients without suspicion of SOD.[24] The most recent RCT examining the effect of indomethacin on PEP found no benefit when compared with placebo in 449 patients.[25] Aside from the differences in study design and sample size, there were significant differences in the underlying patient sample when compared with our study. Their study was 30% patients who were considered high-risk for PEP, while our study included 10% of these patients. Forty percent of both the indomethacin and control groups in their study had pancreatic duct manipulation compared with 20% in our study. Fifteen percent of patients in both the indomethacin and control groups in the prior study had PD stents placed compared with 5% and 3.8%, respectively, in our study. In sum, our study examined a different low-risk patient population. Additionally, we were powered to explore the association between indomethacin and PEP in subgroups including patients with malignant obstruction. In the present study, we found that patients undergoing ERCP for a variety of indications benefit from post-procedural rectal indomethacin, which reduces the rate of PEP and, more specifically, moderate-to-severe pancreatitis, which contributes to the majority of morbidity and mortality associated with PEP.

Patients with pancreaticobiliary malignancy leading to obstruction have traditionally been considered to be low-risk for PEP, particularly in the case of pancreatic adenocarcinoma.[13–15] Small retrospective studies have described the PEP rate as being between 1.5% and 2.5% in this patient population. The purported underlying rationale for this is that in malignant obstruction, chronic obstruction of the pancreatic duct leads to significant ductal and parenchymal atrophy, leading to decreased substrate for potential pancreatitis. Thus, these patients have historically been excluded from trials evaluating rectal administration of NSAIDs. However, in contrast, our study showed relatively high rates of PEP in this population; the overall baseline rates of PEP in unexposed patients with malignant obstruction were 5.87% and 7.53% in unexposed patients with pancreatic adenocarcinoma. Regarding the elevated rate of PEP, there are several possible contributors. Previous studies have found that biliary stenting can increase the risk for PEP, which might explain this elevated rate, as 90% of the patients with malignant biliary obstruction required biliary stent placement compared with 50% of all patients.[28] It is also possible with pancreatic adenocarcinoma that the distortion of the distal common bile duct or the ampullary orifice might have made cannulation more difficult and inadvertent contrast injection and instrument deflection into the PD more likely and/or increased edema with resultant pancreatitis.[29] Among all patients with malignant obstruction, rectal indomethacin showed overall benefit as well as specific benefit in the pancreatic adenocarcinoma subgroup. These findings suggest that PEP is more common in patients with malignant obstruction than previously believed. Future studies examining potential interventions aimed at reducing PEP rates should include this patient population.

Our study is unique in its examination of the effect of rectal indomethacin on PEP in patients representative of real-world practice, including low-risk patients and patients with malignant obstruction. However, this study does have weaknesses inherent to the retrospective cohort design. While there were differences in the background characteristics between the 2 cohorts, we used a multivariable logistic regression analysis to account for these potential confounders. It is possible that there could be additional confounders that we were unable to identify or adjust for. For instance, given the differences in time period in which ERCP was performed in the unexposed and indomethacin exposed groups, differences in endoscopic technique could be a potential confounder, though the operators were all experienced at the onset (see Supplementary Material, "Additional Potential Confounders" in Supplementary Material, and Supplementary Table 3). Our model adjusted for the year of the ERCP and it did not change the impact of indomethacin on the incidence of pancreatitis, suggesting the operator experience and era were not confounders. It is also possible that there were differences in classifying the

outcome of PEP that could introduce bias, as individual endoscopists might have different thresholds to admit patients and further evaluate them. However, given that 5 endoscopists performed the vast majority of ERCPs in both groups, we believe that this risk was low as the post-procedure recovery room policies and follow-up phone calls were standardized. Despite these potential weaknesses, we believe that a retrospective study design is the most suitable way to address this question, given the overall low incidence rate of PEP in this patient population and the need to have a large sample size for any prospective study. Another potential limitation of our study is its external validity. Procedures examined in this study occurred in a tertiary care center where a significant proportion of patients are referred due to prior or expected difficulty with ERCPs at other facilities. The majority of ERCPs were performed by experienced endoscopists at a tertiary care center, which might have limited the effects of variable procedural skills on the risk of PEP. Therefore, generalizability of our findings to other populations may be limited. However, it should be noted that the overall PEP rates in both the unexposed and indomethacin groups were fairly low and similar to large community-based estimates, suggesting that our overall patient population was of similar overall risk.[26,30] Finally, pancreatic duct stents have been proven to provide benefit in patients not receiving indomethacin, but their impact is unclear when patients also receive indomethacin. Our study was not powered to address the role of pancreatic duct stents, given the low usage of pancreatic duct stents (5% and 3.8% in the indomethacin and unexposed groups, respectively) at our institution.

In conclusion, our retrospective cohort study has demonstrated that, in a large population including low-risk patients, administration of rectal indomethacin significantly decreased the rates of PEP as well as rates of moderate-to-severe pancreatitis. Specifically, within our study population, patients with malignant obstruction secondary to pancreatic adenocarcinoma had particularly high rates of PEP at baseline and significantly benefited from indomethacin. Use of rectal indomethacin in current clinical practice is low, as most endoscopists outside of referral centers perform ERCP for indications that are considered low-risk for PEP and, until now, there were no data to support a benefit of rectal NSAIDs in this population.[22] Given this real-world analysis demonstrating clear benefit with rectal indomethacin in a low-risk cohort, our findings suggest a role for increased routine use of post-ERCP rectal indomethacin and the need for additional RCTs investigating rectal indomethacin in specific subpopulations of low-risk patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.04.048.

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Conflicts of interest
The authors disclose no conflicts.

Appendix:

1. Additional Potential Confounders

Year ERCP was performed

As stated in the paper, the year of EPCP performance was included in univariable and multivariable analyses and found not to be a potential confounder of the association between indomethacin administration and post-ERCP pancreatitis (PEP). Additionally, a propensity score matched analysis confirmed the results obtained from the primary analysis, suggesting that receipt of indomethacin was associated with the same magnitude of risk reduction for PEP regardless of year of procedure. Additionally, we performed an analysis to determine if differences exist between patients who had their ERCP performed before and after June 2012, the period after which indomethacin administration was routinely executed at our institution. No patients prior to June 2012 received rectal indomethacin. 1753 patients prior to June 2012 did not receive indomethacin and 4.7% of these patients developed PEP, of which 2.7% developed moderate to severe PEP (Supplementary Tables 1 and 2). After June 2012, 257 patients did not receive indomethacin and 14 (5.5%) of these patients developed PEP, of which 7 (2.8%) developed moderate to severe PEP. 2007 patients received indomethacin after June 2012 and 37 (1.8%) of them developed PEP, of which 11 (0.5%) developed moderate to severe PEP.

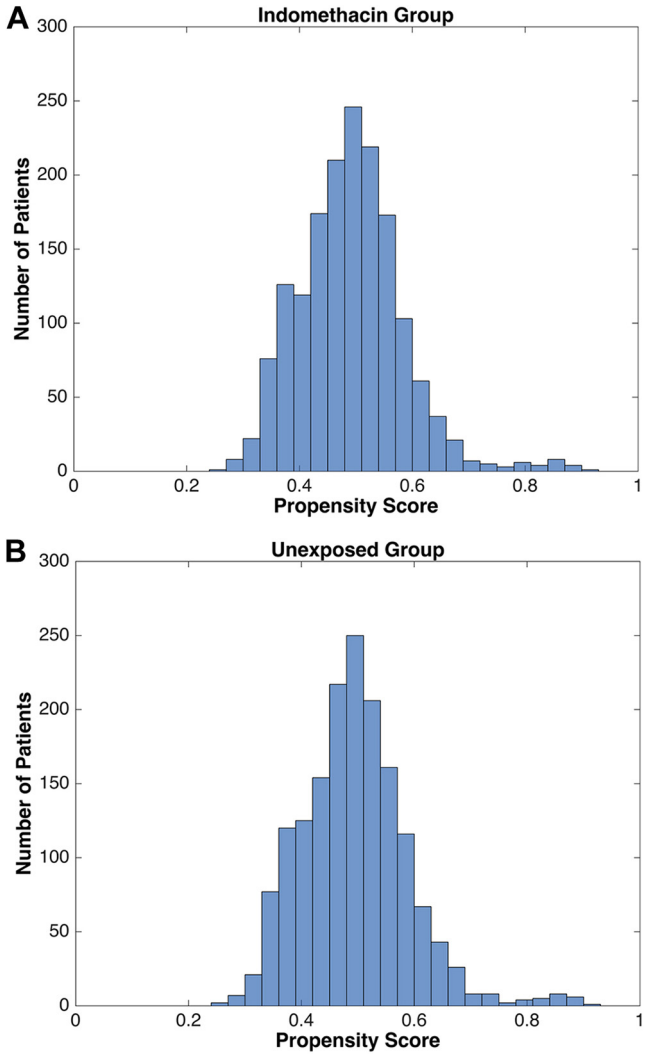
As stated in our paper, our logistic regression model adjusting for PD cannulation and biliary sphincterotomy showed that rectal indomethacin had an adjusted odds ratio (OR) of 0.35 (95% CI 0.24 – 0.51; $p < .001$) for PEP and 0.17 (CI .09 – 0.32) ($p < .001$) for moderate to severe PEP. When this analysis was repeated in patients in receipt of ERCP after June 2012, adjusting for PD cannulation and biliary sphincterotomy, indomethacin reduced the risk of PEP by 86% (OR 0.14, 95% CI 0.06 – 0.30; $p < .001$) and by 92% for moderate to severe PEP (OR 0.07, 95% CI 0.02 – 0.20; $p < .001$). These findings, limited to the post June 2012 era, are consistent with the reduction in risk associated with indomethacin, which was demonstrated over the entire duration of the study.

Individual Endoscopist

The experience of endoscopists performing therapeutic procedures during the study was summarized in Supplementary Table 3. Endoscopist A at our center performed pre-June 2012 era ERCPs but retired and did not perform ERCPs in the post-June 2012 era. Endoscopist F started practicing on July 1, 2011 and was involved for both eras but primarily performed ERCPs in the post-June 2012 era. Two additional endoscopists (I and J), with no prior independent experience, started practicing after June 2012. 5 endoscopists (B-F) performed 88% and 96% of ERCPs for the pre-June 2012 and post-June 2012 eras, respectively. 2nd and 3rd year fellows were not involved in ERCPs at any point during the study period. Advanced endoscopy trainees were involved in a majority of cases and as notated in Table 1 in the paper, there were no differences in the percentage of advanced trainee involvement in ERCPs performed in either treatment group.

2. Propensity-Matched Analysis

As stated in the paper, a secondary propensity score matched analysis was performed comparing the indomethacin exposed and unexposed patients. Propensity scores were generated using covariates associated with indomethacin administration including patient and procedure specific characteristics. The logistic regression model utilized to derive the propensity score included the following 22 variables: age, gender, inpatient status, procedure indication, glucagon usage, antibiotic usage, total bilirubin, prior pancreatitis, prior PEP, pancreatic sphincterotomy, precut sphincterotomy, number of cannulation attempts, ampullectomy, pancreatic brush cytology, biliary sphincterotomy, bile duct stent placement, trainee involvement, balloon dilatation, balloon sphincteroplasty, pancreatic acinarization, endotracheal intubation, type of anesthesia received was performed. Using a caliper of 0.01, one to one matching was employed based on the propensity score. Based on these criteria, a total of 3268 patients, 1634 indomethacin exposed and 1634 unexposed, were included in the propensity score matched analysis. As shown in Supplementary Figure 1, both groups had a similar distribution of propensity scores. ($p = .42$) In the unmatched cohort, as detailed in table 1, there were statistical differences in the baseline characteristic of the indomethacin and unexposed groups including rates of PD stent placement, anesthesia technique, and PD cannulation. As expected in the propensity score matched cohort, the two groups did not differ in the measured characteristics as seen in table 1 (Supplementary Table 4). A multivariable logistic regression analysis was then performed using the propensity score matched cohort. Indomethacin was associated with a 62% reduction in the odds of post-ERCP pancreatitis (OR 0.35, 95% CI 0.23 – 0.52; $p < .001$). Similarly, the propensity matched model adjusted for the year of the procedure showed that indomethacin had an OR of 0.42 (CI 0.22 - 0.84, $p < .001$) for PEP. These results confirm those obtained in the analysis of data from the unmatched cohort.



Supplementary Figure 1. (*A*) Propensity score histograms for indomethacin patients. (*B*) Propensity score histograms for unexposed patients.

Supplementary Table 1. Post-ERCP pancreatitis rates in the unexposed and indomethacin cohorts stratified by time period (prior to June 2012 vs after June 2012)

	No Indomethacin Group			Indomethacin Group		
	Number of Pts.	PEP (%)	Moderate to Severe PEP (%)	Number of Pts.	PEP (%)	Moderate to Severe PEP (%)
2009 - Jun 2012	1753	83 (4.7%)	47 (2.7%)	0	N/A	N/A
Jun 2012 to 2015*	257	14 (5.5%)	7 (2.8%)	2007	37 (1.8%)	11 (0.5%)

*$p < .001$ when comparing indomethacin to unexposed group in patients undergoing ERCP after June 2012.

Supplementary Table 2. Post-ERCP pancreatitis rates in the unexposed and indomethacin cohorts stratified by year of procedure

	No Indomethacin Group			Indomethacin Group		
Time Period	Number of Pts.	PEP (%)	Moderate to Severe PEP (%)	Number of Pts.	PEP	Moderate to Severe PEP
2009	517	25 (4.9%)	14 (2.7%)	0	N/A	N/A
2010	449	18 (4.0%)	10 (2.2%)	0	N/A	N/A
2011	533	27 (5.1%)	15 (2.8%)	0	N/A	N/A
Jan to Jun 2012	254	13 (5.1%)	8 (3.2%)	0	N/A	N/A
Jun to Dec 2012	62	5 (8.2%)	2 (3.3%)	307	6 (2%)	0 (0%)
2013	58	3 (5.2%)	2 (3.5%)	607	10 (1.7%)	3 (0.5%)
2014	80	3 (3.8%)	1 (1.3%)	545	9 (1.7%)	5 (0.9%)
2015	57	3 (5.3%)	2 (2.8%)	549	12 (2.2%)	3 (0.6%)

Supplementary Table 3. A summary of endoscopists involved in the study and their lifetime experience (in years and independent ERCPs performed) prior to June 2012

Endoscopist	Years Performing ERCP prior to the June 2012	Independent Lifetime ERCPs performed before June 2012	Percent of ERCPs performed during January 2009 to June 2012	Percent of ERCPs performed during June 2012 to December 2015
A*	30	9000	8.59%	0.00%
B	16	5500	30.69%	26.53%
C	16	5500	24.15%	21.20%
D	7	3000	16.60%	17.67%
E	14	1200	9.87%	6.39%
F	1	100	6.97%	25.16%
G	5	800	2.99%	0.04%
H	5	1000	0.14%	0.24%
I**	0	100	0.00%	0.98%
J**	13	3000	0.00%	1.18%
K**	0	300	0	0.63%

*This endoscopist stopped performing endoscopies prior to June 2012.
**This endoscopist started performing endoscopies after June 2012.

Supplementary Table 4. Baseline characteristics of propensity matched cohorts. No significant differences between the two groups were found

	Indomethacin Group (N = 1634)	No Indomethacin Group (N = 1634)	*P* value
Patient Characteristics			
Average Age	58 +/- 17	58 +/- 16	.27
Gender (% Male)	975 (60%)	967 (59%)	.94
Inpatient	645 (39%)	657 (40%)	.90
Glucagon Usage	10 (0.6%)	10 (0.6%)	.59
Antibiotic Usage	376 (23%)	392 (23%)	.56
Average Billirubin	3.7 +/- 4.6	3.8 +/- 5.1	.54
History of Pancreatitis	107 (7%)	111 (7%)	.42
Hx of Post-ERCP Pancreatitis	41 (3%)	40 (2%)	.50
Indication			.39
OLT	267 (16%)	341 (21%)	
Gallstone	357 (22%)	320 (20%)	
Malignancy	437 (27%)	409 (25%)	
Bile Leak	133 (8%)	103 (6%)	
PSC	88 (5%)	72 (4%)	
Benign Pancreatic Disease	90 (5%)	82 (5%)	
Benign Biliary Disease	192 (12%)	198 (12%)	
Procedural Characteristics			
Pancreatic Sphincterotomy	36 (2.2%)	38 (2.3%)	.45
Pre-Cut Sphincterotomy	122 (7.5%)	121 (7.5%)	.50
Performance of Ampullectomy	18 (1.1%)	19 (1.2%)	.50
PD Cannulated	309 (18.9%)	302 (18.5%)	.39
Number of Pancreatic Injections	201 (12.3%)	215 (13.2%)	.25
Acinarization	66 (4.0%)	71 (4.0%)	.36
Pancreatic Duct Brushing	10 (0.6%)	12 (0.7%)	.42
Biliary Sphincterotomy	884 (54.1%)	904 (55.3%)	.93
PD Placement	74 (4.5%)	88 (5.4%)	.15
Trainee Involvement	1492 (91.3%)	1485 (90.9%)	.38
Stent Placement	909 (55.6%)	894 (54.7%)	.94
CBD Brushing	351 (21.5%)	346 (21.2%)	.83
Endotracheal Intubation	26 (1.6%)	20 (1.2%)	.23
Sedation with Propofol	0 (0.0%)	11 (0.7%)	.14
Dilatation Performed	321 (19.6%)	301 (18.4%)	.32