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CLINICAL—PANCREAS

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

Nikhil R. Thiruvengadam,[1] Kimberly A. Forde,[2,3] Gene K. Ma,[2] Nuzhat Ahmad,[2] Vinay Chandrasekhara,[2] Gregory G. Ginsberg,[2] Immanuel K. Ho,[2] David Jaffe,[2] Kashyap V. Panganamamula,[2] and Michael L. Kochman[2,4]

[1]Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; [2]Gastroenterology Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [3]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and [4]Center for Endoscopic Innovation, Research and Training, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

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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,