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CLINICAL—PANCREAS

Rectal Indomethacin Does Not Prevent Post-ERCP Pancreatitis in Consecutive Patients

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This article has an accompanying continuing medical education activity on page e19. Learning Objective: Upon completion of this test, successful learners will be able to: (1) define post-ERCP pancreatitis; (2) discuss the efficacy of rectal indomethacin to prevent post-ERCP pancreatitis; (3) identify risk of UGI bleeding among ERCP patients given rectal indomethacin.

See Covering the Cover synopsis on page 782; see editorial on page 805

BACKGROUND & AIMS: Rectal indomethacin, a nonsteroidal anti-inflammatory drug, is given to prevent pancreatitis in high-risk patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), based on findings from clinical trials. The European Society for Gastrointestinal Endoscopy guidelines recently recommended prophylactic rectal indomethacin for all patients undergoing ERCP, including those at average risk for pancreatitis. We performed a randomized controlled trail to investigate the efficacy of this approach. **METHODS:** We performed a prospective, double-blind, placebo-controlled trial of 449 consecutive patients undergoing ERCP at Dartmouth Hitchcock Medical Center, from March 2013 through December 2014. Approximately 70% of the cohort were at average risk for PEP. Subjects were assigned randomly to groups given either a single 100-mg dose of rectal indomethacin (n = 223) or a placebo suppository (n = 226) during the procedure. The primary outcome was the development of post-ERCP pancreatitis (PEP), defined by new upper-abdominal pain, a lipase level more than 3-fold the upper limit of normal, and hospitalization after ERCP for 2 consecutive nights. **RESULTS:** There were no differences between the groups in baseline clinical or procedural characteristics. Sixteen patients in the indomethacin group (7.2%) and 11 in the placebo group (4.9%) developed PEP ($P = .33$). Complications and the severity of PEP were similar between groups. Per a priori protocol guidelines, the study was stopped owing to futility. **CONCLUSIONS:** In a randomized controlled study of consecutive patients undergoing ERCP, rectal indomethacin did not prevent post-ERCP pancreatitis. ClincialTrials.gov no: NCT01774604.

Keywords: Pancreas; NSAID; Inflammation; ESGE Recommendation.

Acute pancreatitis is the most common gastrointestinal indication for admission to the hospital in the United States.[1] Post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most prevalent iatrogenic cause, leading to substantial morbidity, occasional mortality, and a significant economic impact to the US health care system.[2,3] Because of the clinical and economic burden of PEP, extensive research efforts have been devoted to its prevention.[4,5] Among the most promising interventions to prevent PEP is the use of periprocedural rectal nonsteroidal anti-inflammatory drugs (NSAIDs).[6,7]

Rectal NSAIDs are thought to regulate proinflammatory mediators in acute pancreatitis by inhibiting phospholipase A2 activity, including arachidonic acid products and platelet-activating factors.[6,8] One NSAID in particular, rectal indomethacin, has been used extensively since 2012 after the publication of a randomized, placebo-controlled trial in patients undergoing ERCP and considered to be at high risk for PEP.[8] The trial found that a single 100-mg dose of rectal indomethacin significantly reduced the risk of PEP from 16.9% in those receiving placebo to 9.2% in those receiving indomethacin. As a result of this study and others, the European Society for Gastrointestinal Endoscopy in 2014 recommended routine rectal administration of 100 mg indomethacin or diclofenac during ERCP in all patients without contraindication.[9] However, despite these recommendations, the use of rectal NSAIDs in patients not considered to be at high-risk for PEP (the average-risk patient) is unproven.

To determine the benefit of rectal indomethacin in preventing PEP in all patients, we conducted a prospective, randomized, double-blind, placebo-controlled trial in consecutive patients undergoing ERCP.

Materials and Methods

Study Design

We enrolled patients at a single tertiary-care academic medical center in the United States after approval from the

Abbreviations used in this paper: **ERCP, endoscopic retrograde cholangiopancreatography; IRB, institutional review board; NSAID, nonsteroidal anti-inflammatory drug; PEP, post– endoscopic retrograde cholangiopancreatography pancreatitis.**

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Committee for the Protection of Human Subjects (Institutional Review Board [IRB]) at Dartmouth-Hitchcock Medical Center (CPHS#23749). An independent data and safety monitoring board provided regulatory oversight by reviewing blinded subject data, analyzing complications, and performing scheduled in-term analysis. The study was designed under the auspices of the Consolidated Standards of Reporting Trials guidelines.[10]

Patients

The inclusion criteria were defined as consecutive patients undergoing ERCP (± endoscopic ultrasound) at Dartmouth-Hitchcock Medical Center (Lebanon, NH). All patients were adults older than age 18 years who were able to provide written informed consent. Consent was obtained by the therapeutic endoscopist or interventional fellow at the time of informed consent for the procedure. Exclusion criteria included all patients with active acute pancreatitis, those in whom ERCP was performed for diagnosis and/or treatment of acute pancreatitis, contraindication to NSAID therapy (serum creatinine level $>$ 1.4 mg/dL or active peptic ulcer disease), previously documented allergy to NSAIDs, pregnant or nursing mothers, inability to provide written informed consent, those who had been randomized previously within the past 30 days, those younger than 18 years of age, or those without a rectum (ie, status post-total proctocolectomy). Eligible patients who provided written informed consent and met inclusion criteria were randomized after the major papilla was reached and attempts at cannulation were initiated (Figure 1). Randomization was performed in a block format before study initiation by the Dartmouth Investigational Pharmacy, with the investigators blinded to treatment allocation. Premade envelopes with allocation and study number ensured randomization concealment until interventions were assigned.

Intervention

All procedure-related maneuvers and interventions were managed by 2 experienced therapeutic endoscopists. After attempted cannulation, two 50-mg indomethacin suppositories (Cardinal Health, Dublin, OH) or 2 inert placebo suppositories (Letco Medical, Decatur, AL) were administered by the nurse in the procedure room if the patient had met all inclusion criteria and signed written informed consent. The suppository was given per rectum during the ERCP. The endoscopist and patient were blinded to the study allocation.

The number of cannulation attempts, the use and type of pancreatic duct stents, the use of wire-guided cannulation, the amount of periprocedural intravenous fluid, and the participation of an advanced endoscopy fellow were factors all at the discretion of the treating endoscopist and were not outlined specifically in the study protocol.

Outcomes

The primary study outcome was whether 100 mg of rectal indomethacin compared with placebo would decrease the rate of PEP in all patients undergoing ERCP. The secondary outcome was to assess the severity of PEP in those receiving indomethacin vs placebo. PEP was defined if the following 3 conditions were met: new-onset upper-abdominal pain, an increased lipase level greater than 3 times the upper limit of normal 24 hours after the onset of pain, and hospitalization for at least 2 nights. The severity of pancreatitis was defined per the Revised Atlanta Classification.[11]

After ERCP, patients were observed in the recovery area per institutional guidelines for at least 90 minutes. If there was new pain requiring admission, the patient was admitted to the hospitalist medicine service. Subsequent care was left to the discretion of the inpatient service team and supporting gastrointestinal consult service, both of whom were unaware of study-group assignments.

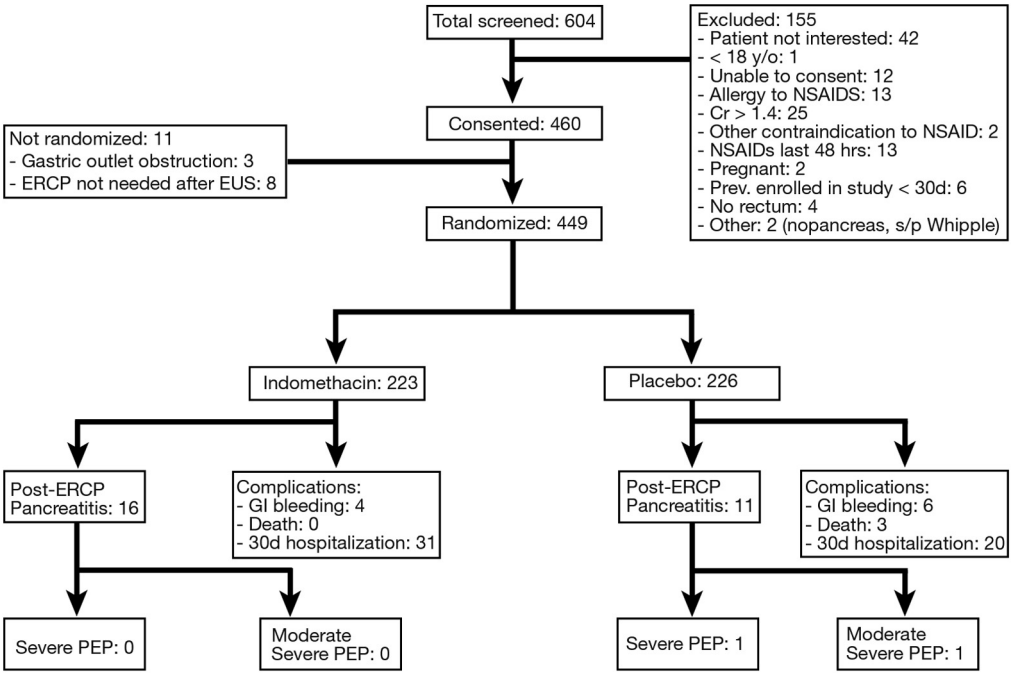

Figure 1. Enrollment and outcomes. GI, gastrointestinal.