Rectal indometacin dose escalation for prevention of pancreatitis after endoscopic retrograde cholangiopancreatography in high-risk patients: a double-blind, randomised controlled trial

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Summary

Background Although rectal indometacin 100 mg is effective in reducing the frequency and severity of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) in high-risk patients, the optimal dose is unknown, and pancreatitis incidence remains high. The aim of this study was to compare the efficacy of two dose regimens of rectal indometacin on the frequency and severity of pancreatitis after ERCP in high-risk patients.

Methods In this randomised, double-blind, comparative effectiveness trial, we enrolled patients from six tertiary medical centres in the USA. Eligible patients were those at high risk for the development of pancreatitis after ERCP. We randomly assigned eligible patients (1:1) immediately after ERCP to receive either two 50 mg indometacin suppositories and a placebo suppository (standard-dose group) or three 50 mg indometacin suppositories (high-dose group). 4 h after the procedure, patients assigned to the high-dose group received an additional 50 mg indometacin suppository, whereas patients in the standard-dose group received an additional placebo suppository. The randomisation schedule, stratified according to study centre and with no other restrictions, was computer generated by an investigator who was uninvolved in the clinical care of any participants, distributed to the sites, and kept by personnel not directly involved with the study. These same personnel were responsible for packaging the drug and placebo in opaque envelopes. Patients, study personnel, and treating physicians were masked to study group assignment. The primary outcome of the study was the development of pancreatitis after ERCP. Analyses were done on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT01912716, and enrolment is complete.

Findings Between July 9, 2013, and March 22, 2018, 1037 eligible patients were enrolled and randomly assigned to receive either standard-dose (n=515) or high-dose indometacin (n=522). Pancreatitis after ERCP occurred in 141 (14%) of 1037 patients—76 (15%) of 515 patients in the standard-dose indometacin group and 65 (12%) of 522 patients in the high-dose indometacin group (risk ratio [RR] 1·19, 95% CI 0·87–1·61; p=0·32). We observed 19 adverse events that were potentially attributable to study drug. Clinically significant bleeding occurred in 14 (1%) of 1037 patients—six (1%) of 515 patients in the standard-dose indometacin group and eight (2%) of 522 patients in the high-dose indometacin group (p=0·79). Three (1%) of 522 patients in the high-dose indometacin group developed acute kidney injury versus none in the standard-dose group (p=0·25). A non-ST elevation myocardial infarction occurred in the standard-dose indometacin group 2 days after ERCP. A transient ischaemic attack occurred in the high-dose indometacin group 5 days after ERCP. All 19 adverse events, in addition to the 141 patients who developed pancreatitis after ERCP, were considered serious as all required admission to hospital. We observed no allergic reactions or deaths at 30 day follow-up.

Interpretation Dose escalation to rectal indometacin 200 mg did not confer any advantage compared with the standard 100 mg regimen, with pancreatitis incidence remaining high in high-risk patients. Current practice should continue unchanged. Further research should consider the pharmacokinetics of non-steroidal anti-inflammatory drugs to determine the optimal timing of their administration to prevent pancreatitis after ERCP.

Funding American College of Gastroenterology.

Introduction

Pancreatitis is the most frequent and potentially devastating complication of endoscopic retrograde cholangiopancreatography (ERCP), accounting for substantial morbidity, occasional mortality, and increased health-care costs.[1–3] Multiple pharmacological agents have been evaluated in the prevention of pancreatitis after ERCP with little success.[4] Rectal non-steroidal

Research in context

Evidence before this study

Pancreatitis is the most common and most feared complication of endoscopic retrograde cholangiopancreatography (ERCP). Rectal non-steroidal anti-inflammatory drugs (NSAIDs)—either indometacin or diclofenac at a dose of 100 mg in the periprocedural period—have been adopted into widespread clinical use to minimise the likelihood of this complication. We searched PubMed, Ovid, and Cochrane Library electronic databases and ClinicalTrials.gov (to identify ongoing trials) between Jan 1, 1990, and June 30, 2019, with the search terms "post-ERCP complications", "post-ERCP pancreatitis prevention", "NSAIDs and pancreatitis", AND "indomethacin and pancreatitis prevention", with no restrictions on study type or language. The pooled estimate from several meta-analyses showed around a 50% risk reduction in high-risk patients. However, the incidence of pancreatitis after ERCP remained at or above 10% in high-risk patients despite the use of NSAIDs. The optimal dose of this phamacoprevention is unknown.

Added value of this study

Rectal NSAIDs have been shown to reduce the incidence of pancreatitis after ERCP in high-risk patients. The primary objective of this study was to determine whether a more aggressive, high-dose indometacin regimen (200 mg) would further lower the risk of pancreatitis. Although this study showed that a high-dose regimen does not appear to offer any advantage over the standard dose (100 mg), the results are important. NSAIDs have been the sole effective pharmacopreventive strategy identified to date to definitively reduce the incidence of pancreatitis after ERCP, and studies to define the optimal dose and timing of administration are needed to refine this intervention. This negative study will help guide the design of future trials aimed at reducing the incidence of this complication.

Implications of all the available evidence

Published guidelines from the American College of Gastroenterology and the American and European Societies for Gastrointestinal Endoscopy support administration of rectal NSAIDs for the prevention of pancreatitis after ERCP in high-risk patients. This study did not show a clear benefit of a high-dose regimen of rectal indometacin, and current practice patterns should continue unchanged. However, further research should consider the pharmacokinetics of NSAIDs to determine the optimal timing of administration to prevent pancreatitis. It is possible that administration of high-dose NSAIDS before ERCP, perhaps given as a single dose, might prove to be more effective than the standard 100 mg dose given after the procedure.

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anti-inflammatory drugs (NSAIDs)—either indometacin or diclofenac at a dose of 100 mg in the periprocedural period—have been adopted into widespread clinical use based on high-quality randomised trials consistently showing around a 50% risk reduction of pancreatitis in high-risk patients. However, the benefit in patients at moderate risk of pancreatitis remains a source of debate.[5–20] Despite this advance, the incidence of pancreatitis after ERCP is 10% or more in high-risk patients, regardless of pharmacoprevention and the placement of a prophylactic pancreatic stent, the only mechanical intervention that reduces the risk of pancreatitis.

When used as an analgesic or anti-inflammatory agent in the management of patients with arthritis, the accepted maximum daily dose of indometacin is 200 mg per day in divided doses. This higher dose of indometacin, which should lead to a higher peak serum concentration, might further lower the incidence of pancreatitis after ERCP. Additionally, since the half-life of indometacin is around 4·5 h, a second dose of the drug might lead to a more sustained effect on the inflammatory cascade. We hypothesised that both dose modifications are important in pancreatitis prevention, and that a regimen consisting of a higher initial dose followed by a second dose (ie, dose escalation) would be superior to the existing standard of treatment. Therefore, we compared modified and standard dose regimens of rectal indometacin for prevention of pancreatitis after ERCP in high-risk patients.

Methods

Study design and participants

In this randomised, double-blind, comparative effectiveness trial of two dosing regimens of rectal indometacin for prevention of pancreatitis after ERCP in high-risk patients, we enrolled patients from six tertiary medical centres in the USA.

The eligibility criteria for this study were intended to select a group of patients at high risk (around 10%) of pancreatitis after ERCP. These criteria were based on patient and procedure-related risk factors that have previously been shown to independently predict pancreatitis.[21] Patients were eligible for inclusion if they met one or more of the following major criteria: clinical suspicion of sphincter of Oddi dysfunction (defined as chronic abdominal pain of suspected biliary or pancreatic origin, accompanied by elevated serum liver tests or pancreatic enzymes or bile or pancreatic duct dilation on abdominal imaging), previous pancreatitis after ERCP, pancreatic sphincterotomy, precut (access) sphincterotomy, more than eight cannulation attempts (as determined by the endoscopist), pneumatic dilation of an intact biliary sphincter, or papillectomy. Patients were also eligible if they met two or more of the following minor criteria: younger than 50 years and female, previous

recurrent pancreatitis (two or more episodes), three or more contrast injections into the pancreatic duct with at least one injection to the tail of the pancreas, pancreatic acinarisation, or pancreatic duct brush cytology.

Patients were ineligible for the study if they met one or more of the following criteria: unwillingness or inability to consent for the study, younger than 18 years (no upper age limit was exclusionary), pregnancy, breastfeeding, standard contraindications to ERCP (eg, uncontrolled coagulopathy or haemodynamic instability), allergy or hypersensitivity to aspirin or NSAIDs, receipt of NSAIDS in the previous 7 days (aspirin 325 mg or less was acceptable), renal insufficiency (serum creatinine >1·4 mg/dL), active or recent (within 4 weeks) gastrointestinal haemorrhage, acute pancreatitis (lipase peak >3 times the upper limit of normal) within 72 h, known chronic calcific pancreatitis, pancreatic head mass, procedure done on major papilla or ventral pancreatic duct in a patient with pancreas divisum (dorsal duct not attempted or injected), ERCP for biliary stent removal or exchange without anticipated pancreatogram, patient with previous biliary sphincterotomy now scheduled for repeat biliary therapy without anticipated pancreatogram, anticipated inability to follow the protocol, or known active cardiovascular or cerebrovascular disease.

Selected patients who did not meet any exclusion criteria were consented for the trial by a clinical research coordinator or one of the investigators, with this consent process occurring before ERCP in the outpatient clinic or the procedure preparation area. At this time, the objectives of the study as well as the risks and benefits of enrolment were explained in detail to potential study participants. Consent from a legal authorised representative was not allowed as per study protocol.

Approval was obtained from the human studies review committee at each participating institution. The study was granted an exemption by the US Food and Drug Administration for an investigational new drug application. The study protocol is available online (appendix pp 1–10).

See Online for appendix

Randomisation and masking

We randomly assigned eligible patients (1:1) to receive either two indometacin suppositories and a placebo suppository, followed 4 h later by another placebo suppository (standard-dose group), or three indometacin suppositories followed 4 h later by another indomethacin suppository (high-dose group). The randomisation schedule was generated centrally at the University of Michigan (Ann Arbor, MI, USA) by an investigator uninvolved in the clinical care of any participants (AKW) using the Stata 12.1 ralloc command, and was stratified according to study centre. There were no additional restrictions placed on sequence generation. The randomisation schedule was provided to the investigational drug service (Medical University of South Carolina; Charleston, SC, USA and University of Michigan) or a research coordinator not directly involved in the trial (at other sites), who then dispensed the assigned suppositories according to the randomisation schedule when informed by the study coordinator that a patient had met eligibility criteria. These same personnel were responsible for packaging the drug and placebo in opaque envelopes. Therefore, assignment to study group was concealed from study participants, treating physicians, and coordinators without knowledge of the next assignment in the sequence.

An identical administration regimen in both groups and the exclusion of investigators and research coordinators (who were involved in the care of the patient and the assessment of outcomes) from placing the suppositories were intended to ensure that study participants, treating physicians, and study coordinators remained masked to study group assignment. However, the success of study masking was not formally assessed.

Procedures

We randomly assigned patients at the conclusion of ERCP because those without a-priori risk factors for pancreatitis could be included in the study based on procedure-related factors that developed. If the endoscopist and research coordinator determined that eligibility criteria had been satisfied, patients were randomly assigned immediately after the procedure to receive either two 50 mg indometacin suppositories and a placebo suppository (standard-dose group) or three 50 mg indometacin suppositories (high-dose group). 4 h after ERCP, patients who were assigned to the high-dose group (having already received 150 mg indometacin) received an additional 50 mg indometacin suppository, whereas patients in the standard-dose group (having already received 100 mg indometacin) received an additional placebo suppository. Although the indometacin and placebo suppositories were not identical, suppositories were administered by clinical nursing personnel who were uninvolved in the post-procedural care of patients or the adjudication of study outcomes.

All ERCP procedures were done under general anaesthesia or monitored anaesthesia care (deep sedation) according to established standards at each site. All procedure-related interventions, including method of cannulation, all therapeutics, and the decision to place a prophylactic pancreatic stent, were left to the discretion of the attending endoscopist. The experience of each endoscopist ranged from 200 to 800 ERCP procedures done on an annual basis. The first dose of indometacin was administered immediately after ERCP while the patient was still in the procedure room. The second dose was administered in the recovery area or in a clinic examination room (if the patient had been discharged and returned later for the second dose). The study protocol did not allow for dose reductions or interruptions. All patients, regardless of study group, received aggressive intravenous fluid administration before and after the procedure in an attempt to minimise

pancreatitis risk, as per institutional practice, unless contraindications were present (eg, history of congestive cardiac failure or liver disease with ascites).

Indometacin suppositories were purchased from G&W Laboratories (South Plainfield, NJ, USA). Except for the Medical University of South Carolina site, which purchased its own indometacin, all suppositories were purchased by the Indiana University clinical research team and then distributed directly to each participating site by Iroko Pharmaceuticals (Philadelphia, PA, USA). Formal potency testing previously confirmed that the vendor provided indometacin suppositories that were pharmacodynamically equivalent.[5]

Most patients were observed in the recovery area after the procedure for 4 h, at which point they received the second study dose of indometacin or placebo. During this observation period, patients in whom abdominal pain developed that was unresponsive to oral analgesics were admitted to the hospital (or for current inpatients, kept in the hospital). A small fraction of clinically well patients were discharged from the recovery area after around 90 min and returned at the 4 h mark to receive the second dose.

Decisions regarding the evaluation and treatment of adverse events after the procedure and in-hospital care were left to the discretion of the endoscopist and treating clinicians, all of whom were unaware of study group assignment. Among patients admitted to hospital, serum amylase and lipase were measured at least once around 24 h after the procedure and subsequently at clinical discretion.

Patients who were discharged after uneventful ERCP were contacted by telephone at 5 days (±2 days) to capture delayed occurrence of the primary endpoint. Patients were contacted again at 30 days (±5 days) to assess delayed adverse events and to determine the severity of pancreatitis after ERCP, which is defined in part by the length of admission to hospital for pancreatitis.[22] No specific follow-up laboratory monitoring was done unless clinically required by a treating physician. Patient demographics, risk factors, ERCP procedural elements, and follow-up data were recorded on standardised data collection forms by a study coordinator who was unaware of study group assignment. Assessment of the primary outcome was centrally reviewed by the study coordinator and primary investigator at the Indiana University site, both of whom were masked to treatment group allocation. Patients could withdraw from the study at any time after signing informed consent, with no criteria for investigator-initiated patient withdrawal. Patients were considered lost to follow-up for the 5-day or 30-day endpoints if repeated efforts to contact them or to obtain their medical records were unsuccessful when the trial ended.

Outcomes

The primary outcome of the study was the development of pancreatitis after ERCP, defined according to the following consensus criteria: new onset (or worsening of baseline) pain in the upper abdomen, elevation in pancreatic enzymes of at least three times the upper limit of the normal range around 24 h after the procedure, and admission to hospital for at least 2 nights.[22] The secondary outcome was the development of moderate or severe pancreatitis after ERCP. Moderate pancreatitis after ERCP was defined as requiring a 4–10 day admission to hospital, whereas severe pancreatitis led to admission to hospital for more than 10 days, or any of the following: intensive care unit stay, development of necrosis, pseudocyst, radiological or surgical intervention, or death. Adjudication of outcome was done by the site research nurse and confirmed by the treating physician, who were both masked to study group allocation, and then forwarded to the central site for confirmation.

Adverse events were defined as reported previously.[22,23] Adverse events that were potentially attributable to the study drug were reported to the local institutional review board and the data safety monitoring board (DSMB). These reportable adverse events were gastrointestinal bleeding, acute kidney injury, allergic reaction, myocardial infarction, cerebrovascular accident, and death.

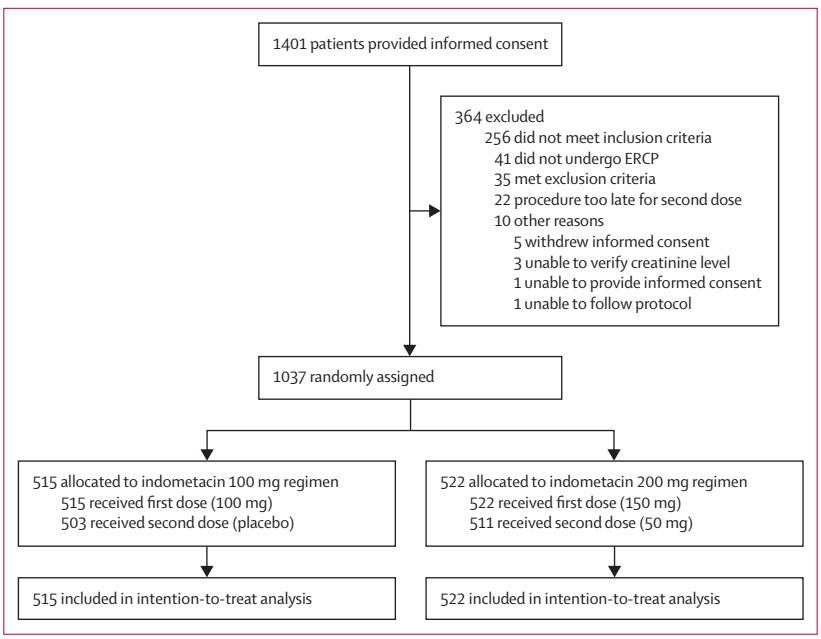

Figure 1: **Trial profile**
ERCP=endoscopic retrograde cholangiopancreatography.

Statistical analysis

Our previous large-scale randomised trial, which compared 100 mg of rectal indometacin with placebo among 602 high-risk patients, used identical eligibility criteria and a similar protocol to this study.[5] That trial reported pancreatitis after ERCP in 27 (9%) of 295 patients in the indometacin group. Thus, in this trial we estimated that 1036 patients (518 per study group) would provide a

	Indometacin 100 mg regimen (n=515)	Indometacin 200 mg regimen (n=522)
Age, years	49·3 (15·2)	50·4 (15·0)
Sex		
Female	392 (76%)	421 (81%)
Male	123 (24%)	101 (19%)
BMI	28·6 (7·03)	29·2 (7·63)
Obese (BMI ≥30)	193 (37%)	198 (38%)
Clinical suspicion of sphincter of Oddi dysfunction	319 (62%)	331 (63%)
Previous pancreatitis after ERCP	77 (15%)	100 (19%)
Previous recurrent pancreatitis	202 (39%)	210 (40%)
Difficult cannulation (>8 attempts)	148 (29%)	146 (28%)
Precut sphincterotomy	71 (14%)	46 (9%)
Double wire cannulation technique	18 (3%)	18 (3%)
Pancreatography		
Patients	446 (87%)	433 (83%)
Number of injections into the pancreatic duct	2·12 (1·63)	1·96 (1·66)
Pancreatic sphincterotomy	245 (48%)	231 (44%)
Placement of pancreatic stent	400 (78%)	393 (75%)
Papillectomy	30 (6%)	32 (6%)
Biliary sphincterotomy	302 (59%)	290 (56%)
Trainee involvement in ERCP	84 (16%)	68 (13%)

Data are mean (SD) or n (%). BMI=body-mass index. ERCP=endoscopic retrograde cholangiopancreatography.

Table 1: **Baseline characteristics**

	Indometacin 100 mg regimen (n=515)	Indometacin 200 mg regimen (n=522)
Gastrointestinal haemorrhage	6 (1%)	8 (2%)
Acute kidney injury	0	3 (1%)
Myocardial infarction	1 (<1%)	0
Transient ischaemic attack	0	1 (<1%)
Allergic reaction	0	0
Death	0	0

Table 2: **Adverse events**

power of at least 80% to detect a 50% reduction in the incidence of pancreatitis after ERCP, from 9% in the 100 mg group to 5% in the 200 mg group, on the basis of Fisher's exact test, with a two-sided significance level of 0·05. This absolute reduction in incidence was thought to be clinically relevant and substantial enough to change existing clinical practice.

For analysis of the primary outcome, we used a two-tailed Fisher's exact test to analyse the difference in the proportion of patients with pancreatitis after ERCP between the two study groups, with a final two-sided p value of less than 0·05 indicating statistical significance. The secondary outcome, the proportion of patients with moderate or severe pancreatitis after ERCP in each study group, was similarly calculated. Both the primary and secondary analyses were done by intention to treat.

When information for the first 400 patients (38% of total enrolment) could be evaluated, we used an ad-hoc rule to trigger a masked interim analysis by the independent DSMB. If more than 66% of pancreatitis or bleeding cases were in a particular group, a formal comparison between groups would be done with a two-sided stopping boundary of 0·005. Similarly, the DSMB recommended a second interim analysis after 600 patients (57% of total enrolment) were evaluated to ensure the safety of patients.

To generate hypotheses regarding patient groups that could particularly benefit from a high-dose indometacin regimen, we did exploratory subgroup analyses on the following prespecified patient and procedural characteristics: age, sex, race, body-mass index, suspicion of sphincter of Oddi dysfunction, previous pancreatitis after ERCP, previous recurrent pancreatitis, difficult cannulation, performance of pancreatography, precut (access) sphincterotomy, pancreatic sphincterotomy, pancreatic acinarisation, biliary sphincterotomy, double wire cannulation technique, pancreatic stent placement, trainee involvement, cardioprotective aspirin use, inpatient versus outpatient status, and participating medical centre. We evaluated all subgroup analyses for interaction effects with indometacin dose by testing for significance of a corresponding interaction term in a multiple logistic regression model.[24]

Statistical analyses were done using STATA version 14.2. The sample size was estimated using STATA 12.1 during the design phase of the trial. An independent DSMB reviewed blinded participant data biannually and conducted two a-priori scheduled interim analyses.

This trial was registered with ClinicalTrials.gov, number NCT01912716.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 9, 2013, and March 22, 2018, 1037 eligible patients, all of whom had data available for analysis (appendix p 11) were enrolled and randomly assigned to receive either standard-dose or high-dose indometacin (figure 1). Patient recruitment was not consecutive because certain factors outside of coordinator or investigator control restricted this approach (eg, procedure done too late in the day to allow for administration of the 4-h drug or placebo, or inability to verify creatinine or lipase level). Three additional patients were enrolled who did not meet eligibility (inclusion) criteria, and one patient had their informed consent signed by their legal authorised representative. Data from these four patients

were not included in the analyses after discussion with the study DSMB. Indications for ERCP included the following (some patients had more than one indication): suspected sphincter of Oddi dysfunction or post-sphincterotomy stenosis (559 patients), choledocholithiasis (57 patients), abnormal liver function tests (132 patients), recurrent acute pancreatitis (381 patients), pancreas divisum (148 patients), papillectomy (68 patients), primary sclerosing cholangitis (eight patients), bile leak (five patients), and several other less frequent indications, and each of these indications were balanced between the two groups. On Feb 9, 2015, and Feb 19, 2016, interim analyses were done by the DSMB to assess the outcomes of the first 400 and 600 patients enrolled in the study, respectively. Both analyses did not meet the predetermined stopping criteria, and recommendations were made to continue the study. Ultimately, 515 patients were randomly assigned to receive the standard dose of rectal indometacin 100 mg whereas 522 were randomly assigned to receive the high-dose rectal indometacin 200 mg. All patients in each group received the immediate post-procedural suppositories. 12 (2%) of 515 patients in the standard-dose group and 11 (2%) of 522 patients in the high-dose group did not receive the 4-h post-procedural suppository (figure 1). Thus, 11 patients in the high-dose group received only 150 mg of indometacin but were analysed according to the intention-to-treat principle. None of these 23 patients who did not receive the second dose did so because of drug-related toxicity, but most commonly chose to leave the recovery area before the 4-h time period had elapsed.

All 1037 patients completed follow-up for the primary endpoint (figure 1) and were included in the analysis. The median follow-up duration for the primary outcome was 5 days (IQR 5–6). Nine (1%) of 1037 patients were lost to follow-up at the 30-day visit and could not be fully assessed for delayed adverse events; three of these nine patients developed pancreatitis after ERCP and thus could not be included in the analysis of the secondary endpoint, leaving 1034 (>99%) patients available for analysis. The median follow-up duration for the secondary outcome and delayed adverse events was 30 days (IQR 29–31). Baseline characteristics, including all inclusion criteria, were similar between the two study groups, except for the proportion of patients with precut sphincterotomy (table 1).

The primary outcome of pancreatitis after ERCP occurred in 141 (14%) of 1037 patients: 76 (15%) of 515 patients in the standard-dose indometacin group and 65 (12%) of 522 patients in the high-dose indometacin group (risk ratio [RR] 1·19, 95% CI 0·87–1·61; p=0·32; table 2).

The secondary outcome of moderate or severe pancreatitis after ERCP occurred in 56 (5%) of 1037 patients: 28 (5%) of 515 patients in the standard-dose indometacin group and 28 (5%) of 522 patients in the high-dose indometacin group (p=1·000; table 2). Four (1%) of 515 patients in the standard-dose group and two (<1%) of 522 patients in the high-dose group had severe pancreatitis after ERCP. Five patients with severe ERCP were admitted to hospital for 10 days or longer and one patient in the high-dose indometacin group

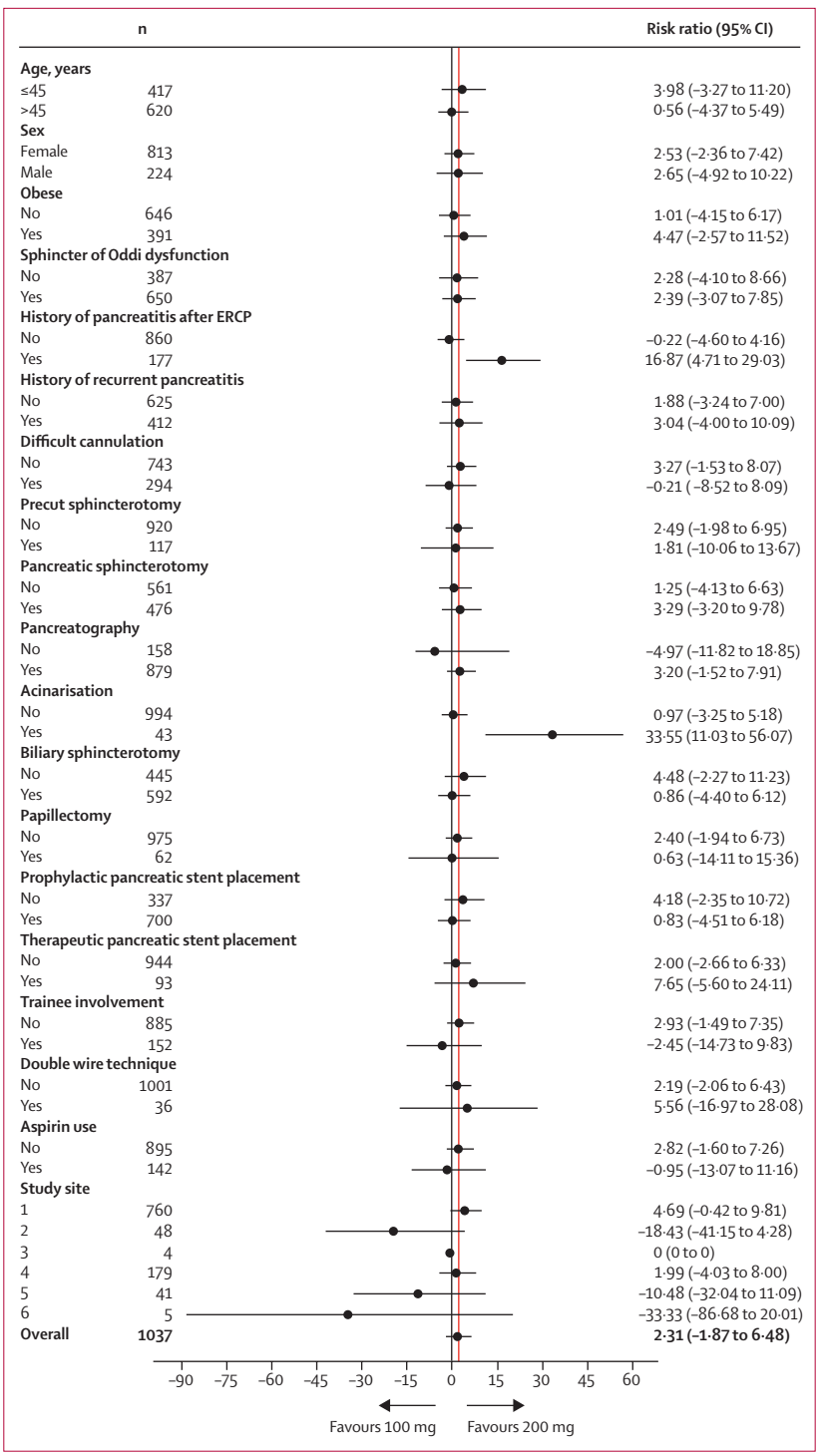

Figure 2: **Subgroup effects on risk difference**
ERCP=endoscopic retrograde cholangiopancreatography.

developed a pancreatic fluid collection that required drainage. We observed no cases of cardiopulmonary organ failure. One patient developed transient renal failure that resolved within 48 h.

Except for patients in whom pancreatic acinarisation occurred or those with a history of previous pancreatitis after ERCP, we observed no significant differences in any of our subgroup analyses (p>0·05; figure 2). We observed a lower incidence of pancreatitis after ERCP associated with the high-dose indometacin regimen in the subgroup of patients who had acinarisation (RR 0·12, 95% CI 0·016–0·87) or a history of pancreatitis after ERCP (0·44, 0·24–0·80).

We observed 19 adverse events that were potentially attributable to study drug (table 2). Clinically significant bleeding occurred in 14 (1%) of 1037 patients, six (1%) of 515 patients in the standard-dose indometacin group and eight (2%) of 522 patients in the high-dose indometacin group (p=0·79). These 14 patients had received a sphincterotomy, and four also underwent papillectomy. Three of the bleeding events required blood transfusion of 2–4 units of packed red cells. All 14 patients underwent repeat upper endoscopic evaluation, with haemostatic manoeuvres required in eight patients. One patient who presented with haematochezia within 24 h of ERCP had a negative follow-up ERCP, and subsequent colonoscopy revealed large haemorrhoids. No patient required angiography or surgery for haemostasis. The median length of hospital stay for these 14 patients was 3 days (IQR 2–4). Three (1%) of 522 patients in the high-dose indomethacin group developed acute kidney injury versus none in the standard-dose group (p=0·25). We considered acute kidney injury as the occurrence of the same degree of renal insufficiency that would have precluded study entry (serum creatinine >1·4 mg/dL). One patient with acute kidney injury presented 20 days after ERCP with dehydration and serum creatinine normalised with intravenous fluid resuscitation. Both the DSMB and institutional review board (IRB) considered this event to be unrelated to study drug. In the second patient with acute kidney injury, the primary inpatient surgical team had decreased the intravenous fluids to maintenance rate only 2 h after ERCP; serum creatinine was 1·46 mg/dL the next day, but returned to baseline the day after with additional intravenous fluids. This event was deemed to be possibly related to study drug by the DSMB but was not reported to the site IRB. The third patient with acute kidney injury developed severe pancreatitis after ERCP. The patient's creatinine increased to 2·3 mg/dL by day 2 after ERCP but decreased to 1·1 mg/dL by day 3 and remained normal thereafter. This event was also reported to the DSMB but not the site IRB. A non-ST elevation myocardial infarction occurred in the standard-dose indometacin group 2 days after ERCP. A transient ischaemic attack occurred in the high-dose indometacin group 5 days after ERCP. All 19 adverse events, in addition to the 141 patients who developed pancreatitis after ERCP, were considered serious as all required admission to hospital. We observed no allergic reactions or deaths at 30 day follow-up.

Discussion

Our findings show that a high-dose treatment regimen of rectal indometacin 200 mg was not more efficacious than the standard 100 mg regimen in reducing pancreatitis after ERCP in patients at increased risk for this complication. Furthermore, we observed no difference in the severity of pancreatitis after ERCP between the standard-dose indometacin and high-dose indometacin groups.

Indometacin shares important pharmacological properties with other NSAIDs and inhibits cyclooxygenase, phospholipase A2, and neutrophil–endothelial interactions, which are all believed to play a major part in the pathogenesis of pancreatitis.[25–27] Although diclofenac undergoes first-pass metabolism with only 50–60% of the drug reaching the systemic circulation as intact diclofenac, indometacin is not subject to substantial first-pass metabolism. The serum concentration of indometacin peaks within 30–90 min after rectal administration and bioavailability is complete.[27,28] This peak concentration is sustained for up to 2 h after administration and then decreases over 4 h.[29] In this study, our high-dose treatment regimen consisted of a higher indometacin 150 mg dose immediately after ERCP, followed by an additional 50 mg 4 h later. When designing the study protocol, we assumed that a higher initial dose might lead to higher therapeutic drug levels, and a second dose might lead to a more sustained effect. However, the entire 200 mg dose given immediately after ERCP, earlier in the cascade of events that occur in pancreatitis (rather than the 150 mg dose followed by the 4-h 50 mg dose), might have led to a more beneficial effect than observed in our study. Alternatively, administration of an NSAID at the beginning of the ERCP or during cannulation rather than at the end of the procedure might further reduce pancreatitis incidence,[8,9] although this point remains controversial and additional randomised trials specifically investigating timing of administration are warranted.[11–14] Pharmacokinetic studies to determine the optimal indometacin regimen and inform future randomised trials are necessary.

The incidence of pancreatitis after ERCP observed in both the standard-dose and high-dose groups exceeded that observed in our previous randomised trial of rectal indomethacin, which had almost identical eligibility criteria.[5] The EPISOD trial,[30] which changed the way in which patients formerly suspected to have type 3 sphincter of Oddi dysfunction are managed, was published 10 months after our current study began, prompting a protocol change that excluded these patients from study entry. However, the interpretation of pain after ERCP and the decision to admit a patient to hospital after the procedure, which are components of the definition of pancreatitis after ERCP, are subjective and vary according to practice styles and institutional policies.

Indeed, practitioners with a lower threshold to admit patients to hospital after ERCP might observe a higher incidence of pancreatitis after the procedure and vice versa. Thus, between-study and between-centre comparisons of pancreatitis after ERCP incidence must be interpreted with caution, as they might reflect a different cohort of centres in the study or secular temporal changes in practice patterns.

793 (76%) of 1037 patients in this clinical trial received a pancreatic duct stent. 700 (88%) patients received a temporary, protective pancreatic duct stent based on their increased risk of pancreatitis after ERCP, and we observed no difference in the incidence of stent placement between the standard indometacin dose and high-dose groups. However, certain patients did not receive temporary stents, either because the endoscopist did not believe this was indicated,[31] or less frequently, because placement was not technically feasible (ansa loop ductal configuration prohibiting wire passage). Regardless of whether a protective stent was placed, we observed no difference in pancreatitis incidence between the standard indometacin dose and high-dose regimens. 93 (12%) of 793 patients who received a pancreatic duct stent had a therapeutic stent placed, typically for management of chronic pancreatitis. Similarly, we observed no difference in pancreatitis incidence between the two indometacin regimens, regardless of whether a therapeutic stent was placed. The results of our study are similar to a recent study from Taiwan.[32] This single-centre, randomised trial of 162 patients also did not show a benefit of double-dose rectal indomethacin 200 mg compared with the standard single dose (4·8% *vs* 9·5%; p=0·24).[32] However, the Taiwanese study investigated a different patient population to our study, recruiting consecutive patients who underwent ERCP for all indications, most of which (144 [89%] of 162 procedures) were done for choledocholithiasis.[32] Furthermore, when considering procedural characteristics,[32] only 42 (26%) of 162 patients were considered at high-risk for post-ERCP pancreatitis, in contrast to our study.

This study has several limitations. Although patients were recruited from six busy US academic centres, 760 (73%) of 1037 patients were recruited from one site, potentially limiting generalisability. We acknowledge that patients with chronic pancreatitis are typically considered to be at a reduced risk of ERCP-induced pancreatitis. However, these patients qualified for study entry because of the presence of additional high-risk features.[21] Furthermore, patients with calcific pancreatitis, a protective factor against pancreatitis after ERCP, were excluded from the study. This study was not designed a priori to determine the benefit of pancreatic duct stent placement versus indometacin alone versus a combination of stent plus indometacin, as is currently being investigated elsewhere.[31] Additionally, aggressive intravenous fluid administration, particularly lactated Ringer's solution, has been shown to have a protective effect against pancreatitis after ERCP.[33,34] Although this recommendation was followed at each site according to institutional and physician practice, a set protocol with type and volume of fluid was not followed or systematically tracked across all sites, as this study began patient recruitment in 2013. Furthermore, established consensus criteria[22] for the definition of pancreatitis after ERCP were used in this study. These consensus criteria have been most commonly used in landmark trials concerning prevention of pancreatitis after ERCP, epidemiological studies, and ERCP guidelines.[35] However, the duration of admission to hospital is a key component of these criteria, which might be confounded by patient pain tolerance and physician practice, among other factors. The revised Atlanta classification of acute pancreatitis consensus definitions stratify pancreatitis severity based on the presence of local and systemic adverse events, including duration of organ failure, rather than duration of admission to hospital.[36] Although not specific for pancreatitis after ERCP, the revised Atlanta classification could provide an alternative for assessing the severity of this complication.[35]

NSAIDs are an interesting option in the prevention of pancreatitis after ERCP as they are easily administered, relatively inexpensive, and have a favourable risk profile when given as a single dose. An initial concern with the current trial was the potential for increased adverse events with the 200 mg dose. However, the observed risk of adverse events that were potentially attributable to indometacin was similar in the standard-dose and high-dose regimens. Specifically, there was no significant difference between the groups in the frequency or severity of bleeding events, consistent with previous reports that NSAIDs (in standard doses) do not increase the rate of post-sphincterotomy bleeding.[3,37] As with our previous randomised trial,[5] patients with contraindications to NSAIDs were excluded from study participation.

In conclusion, escalation to 200 mg of rectal indometacin does not appear to confer an advantage over the standard 100 mg regimen. Pancreatitis after ERCP incidence continued to remain high in high-risk patients despite rectal indometacin treatment. Additional interventions are necessary to further reduce the risk of pancreatitis after ERCP.

Contributors

ELF, GAL, PT, GAC, AKW, SS, GHE, JMS, NMG, and BJE devised the concept for and designed the study. ELF, GAL, PT, GAC, JLW, SS, RSYK, GHE, JJE, DKP, JMS, IIEH, NMG, MAG, LM Jr, ALS, and BJE acquired the data. ELF, AKW, PDRH, and BJE analysed and interpreted the data. ELF and BJE drafted the manuscript. All authors critically revised the manuscript for important intellectual content. ELF obtained the study funding. AKW, PDRH, and BJE did the statistical analysis. ELF, PT, GAC, SES, RSYK, DKP, NMG, and BJE supervised the study. SES, SA, SK, RS, MM, and MH provided administrative and technical support.

Declaration of interests
JJE reports personal fees from Boston Scientific, outside the submitted work. BJE reports personal fees from Takeda Pharmaceuticals, outside the submitted work. NMG reports personal fees from Boston Scientific, outside the submitted work. GAL reports personal fees from Cook Medical and AscentX Medical, outside the submitted work. DKP reports grant support from Boston Scientific, Olympus, Fujifilm, NinePoint Medical, and CSA, outside the submitted work. SS reports personal fees from Boston Scientific, Cook, and Mi-Tech, outside the submitted work. All other authors declare no competing interests.

Data sharing
All data collected during the study, including deidentified participant data and a data dictionary defining each field in the set, will be made available to others with publication of the Article. Additional related documents (eg, study protocol, statistical analysis plan, informed consent forms, and case report forms) will also be made available. These data and forms can be made available following communication with the lead research study coordinator SES (suschmid@iu.edu). Before these data are shared (with professional colleagues or other investigators), the request will be reviewed by the corresponding author ELF. No specific access criteria are required (eg, who has initiated the request, with or without investigator support, and the nature of the proposal), but all proposals must be approved by ELF, with a signed data access agreement in hand before release of the data.

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