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Rectal indomethacin reduces the risk of post-ERCP pancreatitis

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ABSTRACT A clinical appraisal and clinical application of Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med.* 2012;366:1414–22. doi: 10.1056/NEJMoa1111103

Keywords: ERCP, pancreatitis, indomethacin, post-ERCP

Clinical Context

An otherwise healthy 62-year-old man was admitted to the hospital with right upper quadrant abdominal pain, jaundice, nausea and vomiting. Two months prior, he had biliary stricture that was treated with endoscopic retrograde cholangiopancreatography (ERCP) and experienced post-ERCP pancreatitis despite prophylactic pancreatic duct stent placement. During this admission, he was suspected to have recurrent biliary stricture and was scheduled to undergo repeat ERCP.

Clinical Question

Are there any additional measures that can minimize risk of pancreatitis after ERCP in a patient with a history of post-ERCP pancreatitis despite placement of pancreatic duct stent?

Research Article

Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med.* 2012;366:1414–22. doi: 10.1056/NEJMoa1111103

Literature Review

There are an estimated 700,000 ERCP procedures performed annually in the United States.[1] The most significant adverse event associated with this intervention is post-ERCP pancreatitis (PEP), which has been described to occur in about 9.7% of procedures, and 14.7% of procedures in high-risk patients.[2]

Since the early 1990s, prophylactic pancreatic duct stent placement (PSP) has become the standard intervention to prevent PEP. In a meta-analysis by Mazaki et al., PSP was shown to reduce rates of post-ERCP pancreatitis from 19% in the control group to 7% in the stent group.[3] In one account, failed PSP in patients saw PEP in 35% of cases, compared to 13-29% in those where PSP was not attempted.[4]

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At present, there are eight randomized controlled studies and two meta-analyses addressing this topic. The meta-analyses, which used six of eight identical primary studies for analysis, have demonstrated that rectal NSAIDs reduce the risk of PEP by about 50%.[5,6] The largest, well-done, randomized double-blind controlled trial, demonstrating consistent conclusions with the meta-analyses, was chosen for this critical appraisal and clinical application.[7] This paper also had the advantage of testing the efficacy of indomethacin in patients with and without PSP.

Critical Appraisal

The article by Elmunzer et al. is a thoroughly planned randomized controlled study comparing the use of rectal indomethacin administration to placebo in order to assess impact on post-ERCP pancreatitis in high-risk patients. Patients enrolled in the study represent populations of four university-affiliated medical centers in the United States, and likely reflect a similar population from which this paper's clinical question was raised. Patient inclusion criteria identified patients with increased risk of post-ERCP pancreatitis, based on previously validated independent risk factors.[8] The study included 602 randomized patients. A central coordinating office randomly generated group assignments, and stratified groups by study center. Identical-appearing placebo and indomethacin suppositories were administered after ERCP while patient was still in the procedure room. Endoscopists, clinical-service staff, and data-collectors were blinded to study-group assignment. These practices minimize the variation of treatment received by participants in either group.

The primary outcome of interest was post-ERCP pancreatitis. The researchers used a definition consistent with prior literature,[9] "new onset of upper abdominal pain, an elevation of pancreatic enzymes at least three times the upper limit of normal, and hospitalization for at least two nights." A secondary outcome looked at whether this pancreatitis was moderate or severe. All patients that underwent randomization were monitored for 90 minutes after the procedure and serum amylase and lipase were measured within 24 hours. Patients were subsequently contacted within 5 days and after 30 days to assess for any delayed adverse events.[8]

All patients were analyzed in the group to which they were randomized using the intention to treat principle. All patients were accounted for after follow-up. Any adverse events potentially associated with the study were reported. Thirteen adverse events were reported: 11 patients had significant bleeding (4 indomethacin and 7 placebo) and 2 had renal failure (both placebo).

The study found that the indomethacin group had a PEP incidence of 9.2% whereas the placebo group was 16.9%, (p=0.005), meaning the absolute risk reduction was 7.7%. The number needed to treat was 13 based on the study results. More than 80% of patients underwent PSP, and these were equally distributed between the intervention and placebo groups. This means that rectal indomethacin provides additional protection over and above PSP.

The thoroughly organized design of this multicenter, randomized, double-blinded study leads me to believe that the authors' conclusion is valid, and that one dose of rectal indomethacin given immediately after ERCP can significantly reduce the incidence of post-ERCP pancreatitis in high-risk patients. This article provides level 1b evidence using the Oxford and National Guidelines Clearinghouse criteria as a single randomized control trial.

Clinical Application

Similarly to the patients included in the study, my patient was admitted to a university-affiliated medical center in the Midwestern United States. He met the inclusion and exclusion criteria of a history of post-ERCP pancreatitis, pancreatic sphincterotomy, as well as cytologic specimen collection from the pancreatic duct during his previous ERCP. During this hospitalization my patient received both rectal suppository of indomethacin and PSP and despite being high-risk based on his prior history, he did well during this admission and had no evidence of PEP.

Take Home Points
1.) Prophylactic pancreatic duct stent placement is the current standard of care for prevention of post-ERCP pancreatitis.

> 2.) An indomethacin rectal suppository is an inexpensive and easily administered intervention that could be performed at any location that is capable of offering ERCP to its patients. Its favorable risk profile also makes it safe enough that no additional follow up is required above what normally would occur post-ERCP.

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