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Add Pancreatic Duct Stent to Indomethacin to Minimize Post-ERCP Pancreatitis in High-Risk Patients

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PANCREAS

This summary reviews Elmunzer BJ, Foster LD, Serrano J et al. for the SVI Study Group. Indomethacin with or without prophylactic pancreatic stent placement to prevent pancreatitis after ERCP: a randomized trial. Lancet 2024;403: 450-58.

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STRUCTURED ABSTRACT

Question: Is rectal indomethacin non-inferior to rectal indomethacin plus prophylactic pancreatic duct (PD) stent placement for minimizing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in high-risk patients?

Design: Multi-center, prospective, randomized, non-inferiority trial with masking of patients, treating clinicians, and outcome assessors to intervention. Patients enrolled from September 2015 through January 2023.

Setting: Twenty referral centers for complex ERCP in the US and Canada. Over 100 advanced endoscopists of varying experience participated.

Patients: Adults ≥18 years old who had no indication for PD stent placement except pancreatitis prevention and met 1 or more criteria for increased risk of

post-ERCP pancreatitis. Those criteria included: history of post-ERCP pancreatitis, difficult cannulation (defined as at least 6 cannulation attempts or ≥6-minute duration of cannulation), precut sphincterotomy, pancreatic sphincterotomy, short duration (≤1 min) balloon dilation of an intact biliary sphincter or clinical suspicion of sphincter of Oddi dysfunction. Patients could also be enrolled if they met ≥2 minor criteria: female sex and age <50 years old, history of recurrent pancreatitis, or ≥3 PD injections.

Interventions: Patients were randomly assigned (1:1 ratio) to receive two 50 mg indomethacin suppositories peri-procedurally vs two 50 mg indomethacin suppositories peri-procedurally plus prophylactic PD stent placement. All procedure-related interventions, including technical approach to PD stent placement, were at the discretion of the endoscopist. In order to ensure masking, personnel participating in ERCP were precluded from further study patient care for the first 48 hours after ERCP.

Outcomes: Primary outcome was post-ERCP pancreatitis, defined as new onset or increase of abdominal pain, elevation of pancreatic enzymes ≥3X upper limit of normal 24 hours after ERCP, and hospitalization for at least 2 nights. This validated definition was applied as a diagnostic framework by 3 experts at non-enrolling centers who were blinded to patient allocation, and which required agreement by 2 of 3 adjudicators. The secondary outcome was moderate or severe post-ERCP pancreatitis, which also included assessment of radiographic data.

Data Analysis: Intention-to-treat and per-protocol analyses were reported. Non-inferiority margin was defined as 5%. Hence, if there were <5% increased absolute risk of post-ERCP pancreatitis in the upper bound of the 2-sided 95% confidence interval (CI) for the rectal indomethacin alone group, then it would be considered non-inferior to rectal indomethacin plus prophylactic PD stent placement.

Funding: National Institutes of Health.

Results: Among 1950 randomized patients, 38.7% were male, mean age was 55.7 years, and 83.8% were White. Approximately 26%-27% had suspected sphincter of Oddi dysfunction, 82%-84% had difficult cannulation, and 10%-12% required precut sphincterotomy for access. Prophylactic PD stent placement could not be achieved in 19.3% of patients assigned to that group.

Post-ERCP pancreatitis occurred in significantly more patients in the rectal indomethacin alone group vs rectal indomethacin plus prophylactic PD stent placement: 14.9% vs 11.3%; risk difference 3.6%, 95% CI: 0.6-6.6. Since the upper limit of 95% CI for absolute risk difference was greater than 5% (i.e., 6.6%), non-inferiority was not demonstrated. Relative risk difference was 1.32; 95% CI: 1.05-1.66, indicating that high-risk patients had > 30% increased risk of post-ERCP pancreatitis without PD stent placement. Per protocol analysis produced similar findings. Moderate or severe post-ERCP pancreatitis was numerically more frequent for patients in the rectal indomethacin alone group vs rectal indomethacin plus prophylactic PD stent placement: 8.0% vs 6.0%; risk difference 2.1%, 95% CI: -0.2 – 4.3 and post-hoc analysis of pancreatitis-related death identified 3 deaths in the rectal indomethacin alone group vs 0 in the rectal indomethacin plus PD stent: risk difference 0.3%; 95% CI: 0.0-0.7.

COMMENTARY

Why Is This Important?

Post-ERCP pancreatitis is a dreaded complication, which occurs in up to 15% of high-risk patients,[1-2] and leads to hospitalization and even death. Pancreatic duct stent placement, which ensures adequate drainage of the pancreas despite possible edema in pancreatic tissue, minimizes post-ERCP pancreatitis. However, it's time consuming, technically difficult, expensive, and requires subsequent abdominal x-rays to ensure spontaneous passage of the stent. If the stent doesn't pass spontaneously, which occurs in up to 20% of patients, then an EGD is required to remove the stent.

In 2012, a landmark RCT demonstrated that rectal administration of NSAID suppositories decreased post-ERCP pancreatitis[3], and rectal indomethacin is now widely used with ERCP. However, this has also been associated with decreased use of prophylactic PD stent placement.[4-5] Nevertheless, the American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend rectal indomethacin PLUS prophylactic PD stent placement for high-risk patients, although Level 1 randomized controlled trial (RCT) evidence to support this was lacking.

With the publication of this seminal RCT, Level 1 evidence supporting this guideline recommendation is now available. This is a particularly elegant study. The investigators did not limit study endoscopists to expert biliary endoscopists at a few high-volume centers. Instead, over 100 advanced endoscopists with varying skill levels and years of experience participated, which enhances generalizability of study results. Masking was enforced by excluding ERCP team personnel from study patient care for 48 hours after ERCP and by having an outside panel of 3 expert endoscopists interpret clinical and laboratory data to determine if post-ERCP pancreatitis

occurred using a standardized definition. Almost 2000 patients were enrolled over 8 years to provide an adequate sample size to assess for non-inferiority. Ultimately, the study demonstrated that rectal indomethacin alone increased the risk of post-ERCP pancreatitis by more than 30% compared to rectal indomethacin plus prophylactic PD stent placement in high-risk patients.

Key Study Findings

Post-ERCP pancreatitis occurred in significantly more patients in the rectal indomethacin alone group vs rectal indomethacin plus prophylactic PD stent placement: 14.9% vs 11.3%; risk difference 3.6%, 95% CI: 0.6-6.6.

Caution

PD stent placement procedures were not standardized, including selection of PD stent, and duration and number of attempts at PD stent placement. This is understandable since there is no standard of care to prophylactic PD stent placement. In fact, PD stent placement failed in approximately 20% of patients assigned to this group, but the per-protocol analysis was similar to the ITT analysis. This indicates that failure to successfully place prophylactic PD stents did not increase risk of post-ERCP pancreatitis. Also, approximately 500 study patients underwent ERCP for possible sphincter of Oddi dysfunction (SOD) and SOD manometry is high-risk for post-ERCP pancreatitis. However, the utility of diagnosing and then treating these patients with sphincterotomy is increasingly controversial.

My Practice

Since I am not an interventional endoscopist, I consulted with the lead author of the study, B. Joseph Elmunzer, MD, MSc, about his practices. He performs PD stent placement plus rectal indomethacin in all patients at high-risk for post-ERCP pancreatitis. He also boluses most patients with 2.5-3.0 liters of lactated ringer's (LR) solution intravenously (IV) during the peri-procedural period unless they are elderly and/or have cardio-vascular or pulmonary disease. As Dr. Elmunzer emphasized, this has not yet been demonstrated to minimize post-ERCP pancreatitis in well-designed RCTs.

He gives rectal indomethacin to virtually all ERCP patients to minimize post-ERCP pancreatitis, regardless of risk. However, since the cost of rectal indomethacin has risen precipitously, he may hold it in selected patients at very low risk, such as some patients with prior sphincterotomy who are getting uncomplicated bile duct stent changes.

For Future Research

Optimal approaches to PD stent placement, including type of stent, should be explored and additional preventive treatments, including bolus intravenous lactated Ringer's solution to minimize post-ERCP pancreatitis should be identified.

Conflicts of Interest

Dr. Schoenfeld reports no financial conflicts of interest.

Note: The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary.

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REFERENCES

1. Kaimakliotis P, Kochman ML. Prophylactic pancreatic stent placement to prevent pancreatitis after ERCP. Lancet 2024; 403: 411-13.
2. Buxbaum JL, Freeman M, Amateau SK, et al. ASGE guideline on post-ERCP pancreatitis prevention strategies: summary and recommendations. Gastrointest Endosc 2023;97:153-62.
3. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414-22.
4. Smith ZL, Elmunzer BJ, Cooper GS, Chak A. Real-world practice patterns in the era of rectal indomethacin for prophylaxis against post-ERCP pancreatitis in a high-risk cohort. Am J Gastroenterol 2020;115:934-40.
5. Ashat M, Kandula S, Cote GA, et al. Utilization pattern of prophylactic measures for prevention of post-ERCP pancreatitis: a national survey study. Gastrointest Endosc 2023;97:1059-66.