

ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

Section Editor: John Baillie, MB ChB, FRCP

Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis



Vikesh K. Singh, MD, MSc
 Director, Pancreatitis Center
 Medical Director, Pancreatic Islet Autotransplantation Program
 Associate Professor of Medicine
 Division of Gastroenterology
 Johns Hopkins Hospital
 Baltimore, Maryland

G&H How common is the development of pancreatitis following endoscopic retrograde cholangiopancreatography?

VS The incidence of pancreatitis post-endoscopic retrograde cholangiopancreatography (ERCP) varies between 2% and 15%. The incidence rates reported in earlier studies were limited by their retrospective design, the inclusion of patients with variable risks for developing post-ERCP pancreatitis (PEP), and differences in the definition of PEP.

G&H What accounts for the higher incidence of PEP after the year 2000?

VS The higher incidence of PEP after the year 2000 may be due to the transition from ERCP being both diagnostic and therapeutic to being a primarily therapeutic procedure. Because noninvasive imaging modalities have replaced diagnostic ERCP, this procedure is now predominantly reserved for patients with a high probability of requiring therapeutic intervention. However, therapeutic ERCP carries a higher risk of PEP over diagnostic ERCP, which may have led to the higher incidence of PEP after the year 2000. Prophylactic measures such as pancreatic stents and nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly used; however, these measures did not become the standard of care until recently. Rectal NSAIDs received increased attention only

after the landmark study by Dr B. Joseph Elmunzer and colleagues that was published in 2012. It will be interesting to follow the trend of PEP now that these prophylactic measures are being increasingly used.

G&H How have the results of the EPISOD study altered clinicians' understanding of PEP?

VS The results of the EPISOD (Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction) study emphasize the importance of avoiding an ERCP in patients with suspected sphincter of Oddi dysfunction (SOD), as it has been established that patients with suspected SOD are at a higher risk of developing PEP despite the use of prophylactic pancreatic duct stenting. Alternative noninvasive diagnostic procedures, such as endoscopic ultrasound, magnetic resonance imaging, or magnetic resonance cholangiopancreatography, should be considered in place of ERCP whenever possible. In a situation in which patients with SOD Type I or II require an ERCP, the procedure should be performed only by expert endoscopists at a tertiary center.

G&H What is the association between suspected SOD Type II and idiopathic recurrent acute pancreatitis?

VS There is a significant overlap between patients with suspected SOD Type II and idiopathic recurrent acute

pancreatitis (IRAP), although this overlap was not represented by the participants in the EPISOD study. A randomized trial conducted by Dr Gregory A. Coté and colleagues demonstrated that even among patients with IRAP with pancreatic SOD confirmed by sphincter of Oddi manometry (SOM), there is no significant advantage of pancreatic over biliary sphincterotomy. Furthermore, patients with pancreatic SOD had a higher incidence of recurrent acute pancreatitis compared with patients with a normal SOM following ERCP. Therefore, ERCP should be avoided in this patient population, and other noninvasive options (as mentioned previously) should be considered. Data are increasingly showing that patients with IRAP have an underlying genetic mutation, and it is not clear whether ERCP will prevent episodes of recurrent acute pancreatitis.

G&H What other noninvasive methods are available to gauge biliary and pancreatic pressures in order to avoid the risk of direct measurement?

VS Animal studies have shown that water-perfusion catheters used for SOM initiate the PEP cascade. Human studies have not unequivocally established SOM as an independent risk factor for PEP. However, any trauma to the duodenal papillae that leads to pancreatic ductal outflow obstruction should be avoided, as this can lead to PEP.

SOM is the gold standard for measuring biliary and pancreatic pressures to diagnose SOD. There are several experimental techniques being studied that are noninvasive or potentially less invasive. One technique is secretin-stimulated magnetic resonance cholangiopancreatography, which was compared to SOM and shown to have a diagnostic accuracy of 73% for SOD Type II and 46% for SOD Type III. Functional magnetic resonance imaging with gadoxetate disodium is another technique, although it may not be applicable to postcholecystectomy patients. Hepatobiliary scintigraphy using technetium-99m-labelled dyes can assess delay in biliary drainage but can have variable results and has only a supportive role in the evaluation of SOD. Optical coherence tomography, which utilizes low-power infrared light to highlight the details of the microstructure of the gastrointestinal wall, is similar to ultrasound but still requires ERCP and cannulation. Endolumenal Functional Lumen Imaging Probe (EndoFLIP, Crospon Medical Devices) is a technique that measures the distensibility of SOD, describes the motility pattern of the sphincter, and is potentially less traumatic than conventional SOM. However, none of the modalities described above have been well established in comparison to SOM nor are they yet the standard of care.

G&H What changes in PEP data may be seen now that SOM is no longer performed for SOD Type III?

VS SOD is a major risk factor for the development of PEP independent of whether SOM is performed. This conclusion was further supported by a systematic review that my colleagues and I conducted, in which 5 of 6 randomized, controlled trials (RCTs) evaluating the risk of PEP reported SOM to be a risk factor. However, none of the RCTs in our review showed SOM to be an independent risk factor for PEP on multivariable analysis, which suggests that other factors, such as cannulation difficulty or SOD itself, are the predominant factors that increase the risk of PEP.

The results of the EPISOD study demonstrate that sphincterotomy is no more effective than sham among patients with suspected SOD Type III. Given the very significant increase in the risk of PEP in patients with SOD Type III, it is hard to justify ERCP in this situation, and most endoscopists have stopped performing it.

G&H What were the key findings of your systematic review of the placebo or no-stent arms of RCTs on PEP?

VS My colleagues and I conducted a systematic review of placebo or no-stent arms of RCTs with the aim of reporting the incidence, severity, and mortality of PEP. Our review included 108 RCTs with a total of 13,296 patients. The overall PEP incidence was 9.7%, and the mortality rate was 0.7%. The severity of PEP was mild, moderate, and severe in 5.7%, 2.6%, and 0.5% of patients, respectively. Additionally, the incidence of PEP in high-risk patients was 14.7%, with a 0.2% mortality rate. Of note, the incidence of PEP was 13.0% in North American RCTs compared with 8.4% and 9.9% in European and Asian RCTs, respectively.

G&H What were the limitations of your review?

VS The key limitation of our review was heterogeneity among the included RCTs, as the participants were not adequately stratified into high- and average-risk subgroups in 39% of the included RCTs. Furthermore, even among the high-risk RCTs, the criteria for defining a participant as high risk were weighted equally because it is not known whether a higher number of criteria increases the risk of PEP in a linear vs exponential manner. In addition, the rates of PEP were obtained from RCTs, which are more likely to be conducted at tertiary referral centers that employ expert endoscopists whose procedural case mixes tend to be more complex.

G&H Is SOD more prevalent in North America than in Europe or Asia?

VS It is unclear whether SOD is actually more prevalent in North America or if it is more frequently established in North America due to the increased use of SOM. If SOD is, in fact, more prevalent in North America, the higher incidence of PEP may be explained. It should be noted that SOD is typically not an indication for ERCP in Europe and Asia, which may explain the lower rates of PEP in those areas. Even if SOD is prevalent globally, it may not be diagnosed as such due to its overlap with other functional disorders and IRAP.

G&H What are the priorities of research in this field?

VS Research is needed to determine whether the risk of PEP increases in a linear or exponential manner based on the number and weight of individual patient and procedural risk factors. Additionally, studies should further clarify the role of ERCP in SOD Types I and II as well as the role of IRAP in both standard pancreatic ductal anatomy and in patients with pancreas divisum. More data are needed to define whether medical and pharmacologic prophylactic regimens, alone or in combination, could potentially replace pancreatic stents. There is an ongoing multicenter, noninferiority trial funded by the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases that is comparing rectal indomethacin and pancreatic stent placement vs rectal indomethacin alone for the prevention of PEP.

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Dr Singh has no relevant conflicts of interest to disclose.

Suggested Reading

Corwin MT, Lamba R, McGahan JP. Functional MR cholangiography of the cystic duct and sphincter of Oddi using gadoxetate disodium: is a 30-minute delay long enough? *J Magn Reson Imaging*. 2013;37(4):993-998.

Coté GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. *Gastroenterology*. 2012;143(6):1502-1509.e1.

Elmunzer BJ, Scheiman JM, Lehman GA, et al; US Cooperative for Outcomes Research in Endoscopy (USCORE). A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med*. 2012;366(15):1414-1422.

Elmunzer BJ, Serrano J, Chak A, et al; SVI study group and the United States Cooperative for Outcomes Research in Endoscopy (USCORE). Rectal indomethacin alone versus indomethacin and prophylactic pancreatic stent placement for preventing pancreatitis after ERCP: study protocol for a randomized controlled trial. *Trials*. 2016;17(1):120.

Kochar B, Akshintala VS, Afghani E, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. *Gastrointest Endosc*. 2015;81(1):143-149.e9.

Kunwald P, Drewes AM, Kjaer D, et al. A new distensibility technique to measure sphincter of Oddi function. *Neurogastroenterol Motil*. 2010;22(9):978-983, e253.

Pereira SP, Gillams A, Sgouros SN, Webster GJ, Hatfield AR. Prospective comparison of secretin-stimulated magnetic resonance cholangiopancreatography with manometry in the diagnosis of sphincter of Oddi dysfunction types II and III. *Gut*. 2007;56(6):809-813.

Singh P, Gurudu SR, Davidoff S, et al. Sphincter of Oddi manometry does not predispose to post-ERCP acute pancreatitis. *Gastrointest Endosc*. 2004;59(4):499-505.

Sostre S, Kalloo AN, Spiegler EJ, Camargo EE, Wagner HN Jr. A noninvasive test of sphincter of Oddi dysfunction in postcholecystectomy patients: the scintigraphic score. *J Nucl Med*. 1992;33(6):1216-1222.