

# ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

Section Editor: John Baillie, MB ChB, FRCP

## Recent Research on Sphincter of Oddi Dysfunction



Joseph Romagnuolo, MD  
Palmetto Health, Columbia Gastroenterology Associates  
Columbia, South Carolina

### G&H What is sphincter of Oddi dysfunction?

**JR** Persistent or recurrent right upper quadrant (RUQ) unexplained abdominal pain after cholecystectomy is a common problem, especially in patients who had their gallbladder removed without evidence of gallstones or patients whose original symptoms (constant pain, crampy pain, and bloating) were atypical for biliary colic. For an unclear reason, 90% of these patients are female. The sphincter at the bottom of the biliary and pancreatic ducts has been blamed for this pain in some patients (ie, sphincter of Oddi dysfunction [SOD] or spasm/stenosis). It is rationalized that, although SOD likely preceded the cholecystectomy, the symptoms may appear or worsen after removal of the gallbladder (which took up the slack of the excess bile under pressure behind the obstructed sphincter). Although there have recently been questions about the importance of the classification of SOD in terms of predicting symptom response, there have traditionally been 3 types of SOD, which depend on the amount of objective evidence supporting biliary obstruction as the cause for pain: Type 1 SOD consists of biliary dilation and abnormal liver enzymes, type 2 SOD consists of dilation alone or abnormal enzymes alone (ideally temporally associated with pain attacks), and type 3 SOD consists of pain alone, with normal laboratory tests and imaging.

### G&H How effective is traditional management?

**JR** Response to biliary sphincterotomy is thought to be up to 100% in (biliary) type 1 SOD, 80% to 90% in (biliary) type 2 SOD with abnormal manometry, and unclear for type 3 SOD (perhaps 50%-70%). Although the usefulness of manometry in suspected type 1 and 3 SOD has been questioned for selecting patients more likely to respond to sphincterotomy, 2 randomized trials (one Australian and one American) showed that patients with clinically suspected type 2 SOD with normal manometry had a response to biliary sphincterotomy that was similar to that of the sham groups

(30%-40%); therefore, it appears that manometry is important in this subtype. A 2002 National Institutes of Health consensus paper highlighted that, although patients with type 1 SOD could be treated without manometry, with empiric sphincterotomy, patients with type 2 SOD should only be treated with manometry, and patients with type 3 SOD should not be treated outside of an academic/research setting.

Manometric confirmation of SOD (in clinically suspected patients) requires documentation of basal sphincter pressures over 40 mmHg (generally in 2 leads in the perfusion system, measuring pressures on 2 different sides of the catheter, in order to avoid artifactual positives from leaning the catheter on one side of the sphincter during measurement). Other manometric findings (high amplitude contractions, frequent contractions, and retrograde contractions), which are sometimes referred to as dyskinesia, were not predictive of outcomes in the Australian trial. In contrast, basal pressure over 40 mmHg (what the Americans called "SOD" and what the Australians called "stenosis") was predictive. Nuclear medicine tests (hepatobiliary iminodiacetic acid scans) for bile duct drainage were performed in a subset of patients in both trials and were not predictive. Although a few studies in highly selected patients showed that these scans could correlate with manometry, many studies do not. As such, there is no good noninvasive test to predict manometry results.

Topics of debate include how high enzymes have to be, whether they have to be timed with attacks (abnormal during pain and normal when pain resolves), and what constitutes typical pain (constant vs intermittent, relationship to meals, and presence of nausea, bloating, or other irritable bowel syndrome [IBS] symptoms). Because fatty liver is currently common in the general population, mild liver enzyme elevations are often thought to be incidental to the pain and create a diagnostic dilemma. Also, diagnostic endoscopic retrograde cholangiopancreatography (ERCP) in patients with suspected SOD has up to a 20% chance of causing post-ERCP pancreatitis. Although this complication is only rarely severe or fatal and can be reduced to 10% to 15% by using tempo-

rary small-caliber pancreatic stenting (and even further with pharmacoprevention), it still represents a considerable risk.

### G&H What prompted the EPISOD study, and what were the goals of this study?

**JR** It was clear that patients with suspected type 3 SOD were the most common SOD subcohort (given that this type did not require objective findings), yet these patients had the least evidence for therapy (or even for the benefit of ERCP/manometry investigation). In addition, some patients were receiving ERCP in the community for type 3 SOD-like situations (to rule out the presence of a stone when having pain but little objective findings) and were being empirically treated. For this reason, the EPISOD (Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction) trial received a planning grant from the National Institute of Diabetes and Digestive and Kidney Diseases over 10 years ago. After years of planning, especially developing and validating an outcomes tool that could measure pain burden in patients with intermittent pain, the trial was completed and the results were recently published by me and my colleagues.

The goal of this randomized, sham-control trial was to determine whether sphincterotomy helped patients with postcholecystectomy biliopancreatic-type pain (unexplained epigastric/RUQ pain) who had few objective findings. Patients and outcome assessors were blinded. Secondary goals included examining the role of manometry in predicting success, as patients were randomized to sphincterotomy or sham independent of their manometry results. We also wanted to know whether pain features, demographics, and coexisting depression, anxiety, coping disorders, or IBS would predict a higher or lower response. Lastly, in pancreatic manometry-positive patients randomized to sphincterotomy, we wanted to see whether biliary sphincterotomy was sufficient or if dual sphincterotomy added benefit. (These patients were randomized further to 1 of these groups.) The primary outcome measurement was performed using the Recurrent Abdominal Pain Intensity and Disability index, a measure based on a tool used to quantify pain-related disability from migraines. Patients who used regular narcotics in the past 3 months or required an intervention before 12 months were also considered failures. Patients who were otherwise eligible but refused randomization were followed in an observational cohort (EPISOD2).

### G&H What were the results of this study?

**JR** Twenty-seven patients (37%; 95% CI, 25.9%-48.1%) in the sham treatment group vs 32 patients (23%; 95% CI, 15.8%-29.6%) in the sphincterotomy group experienced successful treatment (adjusted risk difference, -15.6%; 95% CI, -28.0% to -3.3%;  $P=.01$ ). Among patients with pancreatic sphincter hypertension, 14 (30%; 95% CI, 16.7%-

42.9%) who underwent dual sphincterotomy and 10 (20%; 95% CI, 8.7%-30.5%) who underwent biliary sphincterotomy alone experienced successful treatment. Approximately one-third of patients underwent repeat ERCP interventions in both groups ( $P=.22$ ). Pancreatitis occurred in 11% of the sphincterotomy group and 15% of the sham group. Non-randomized patients in EPISOD2 (manometry-directed standard care) had similar response rates: 24% after biliary sphincterotomy and 31% after dual sphincterotomy, while 17% did not undergo sphincterotomy (usually due to normal manometry).

Manometry results were not associated with the outcome. No clinical subgroup appeared to benefit from sphincterotomy more than other subgroups. Patients who had mildly elevated liver or pancreas enzyme levels were no more likely to respond.

### G&H What were the limitations of this study?

**JR** Patients were recruited from 7 tertiary centers, which is important to note because patients seen in a tertiary center are often different from those seen in the community. (Patients may be selected for referral to a tertiary center due to psychological profile, financial and social situation, comorbidities, or atypia of symptoms.) The outcome assessment was stricter than that used in prior studies (as prior studies used subjective feeling of improvement as their outcome measure); however, even when the criteria were loosened as a secondary analysis, the same conclusions were reached.

### G&H What are the implications of this study?

**JR** It seems clear that patients with postcholecystectomy pain who are being considered for ERCP with or without manometry, who have little or no objective signs of obstruction, have no incremental chance of improvement over placebo/sham. Despite tertiary experts performing these procedures and near-universal use of temporary pancreatic stents (which were successful in all but 1 patient), post-ERCP pancreatitis rates remained considerable (10%-15%).

The adverse event rate may be even higher with non-experts. In the community, these patients are sometimes referred for an ERCP to rule out the presence of stones despite having normal magnetic resonance imaging/magnetic resonance cholangiopancreatography results and near-normal laboratory test results, and pancreatic stents are not often inserted for protection. In reality, these patients are likely better labeled as having suspected SOD, given that they have pain without laboratory tests or imaging to support the presence of obstruction, and would be predicted to have similarly poor response rates. No unexpected bile duct stones were found in our study, so community ERCP physicians who do not perform manometry still need to pay attention to the study results.

## G&H Based on these findings, how should patients with SOD be managed?

**JR** Patients with type 1 or 2 SOD should be managed as before, although perhaps only the suspected type 2 SOD patients with marked enzyme elevations or dilation on imaging should be considered eligible for manometry-directed therapy, given that the patients with minimal lipase and liver enzyme elevations (<2 times) had the same low benefit as patients with normal laboratory test results. The EPISOD trial also suggests that type 3 SOD does not appear to exist, so patients with so-called suspected type 3 SOD should not undergo ERCP, with or without manometry; this treatment does not appear to help, and the number needed to harm is only 7 to 10.

## G&H Are there alternative treatment options?

**JR** There does not appear to be a reliable surrogate for manometry in these patients, and even if there were, manometry is not predictive of response, so such a test would not be helpful. The same argument may hold true for intrasphincteric onabotulinumtoxinA (Botox, Allergan) when used as a diagnostic test, even though some preliminary studies had shown promise.

A number of narcotic-sparing neuromodulating drugs (eg, tricyclic antidepressants) have been used to varying degrees in functional epigastric pain and functional dyspepsia (what the syndrome of postcholecystectomy pain likely represents) and should be tried. However, more study is needed in this area. For intermittent pain, antispasmodic agents are reasonable. Proton pump inhibitors and agents to eradicate *Helicobacter pylori* infection have some efficacy for functional dyspepsia, albeit with a high number needed to treat, and are reasonable to try. Gastric emptying studies, which can identify more objective signs of an upper gastrointestinal (GI) neuropathy, can be helpful, especially when nausea, bloating, and early satiety coexist with pain.

## G&H Should there be an overhaul of SOD classification?

**JR** This is certainly an issue of debate. A recent study showed little correlation between the type of SOD and the response rate in a nonrandomized cohort. In addition, patients with minor liver/pancreas enzyme elevations in the EPISOD study (patients with type 2 SOD in some people's minds) did just as poorly as patients with type 3 SOD. Patients with remote cholecystectomies (in whom the bile duct is assumed to have gradually dilated with time after surgery) and with a history of long-term narcotic use (which is associated with biliary dilation) may have other explanations for biliary dilation, and fatty liver may explain many serology-negative patients with mild

liver enzyme elevations. These patients may masquerade as patients with type 1 SOD yet have as little of a response as patients with type 3 SOD.

## G&H Could these patients have other causes for their symptoms, such as gut motility disorders?

**JR** Yes, it is presumed that these patients likely have visceral hypersensitivity syndromes of the upper GI tract. The pain is likely GI neuropathic in origin, with associated sensory, and sometimes motor, abnormalities. The pain may be constant but may be exacerbated by food touching or distending the stomach or duodenum with meals.

## G&H What are the next steps in research?

**JR** Type 3 SOD skeptics will likely be satisfied with the EPISOD study confirming their suspicion that postcholecystectomy pain with no objective findings is not helped by ERCP or sphincterotomy. Type 3 SOD believers, especially those who have seen dramatic responses in some patients, may want another confirmatory study; however, it is unlikely that the rigor of the EPISOD study will be replicated in another randomized trial of suspected type 3 SOD. Those dramatic responses have been known to occur following therapies that are no better than sham, which likely explains anecdotal experiences. There may be medicolegal implications for physicians who continue the practice of type 3 SOD investigation and treatment in light of the EPISOD results (except perhaps in patients being investigated for restenosis after prior treatment).

It appears most important to focus future efforts on better medical and/or behavioral therapies for functional epigastric pain and on research (perhaps epidemiologic) examining the causes of this presumed neuropathic pain syndrome.

*Dr Romagnuolo is a consultant for Olympus and Cook Medical.*

## Suggested Reading

Brawman-Mintzer O, Durkalski V, Wu Q, et al. Psychosocial characteristics and pain burden of patients with suspected sphincter of Oddi dysfunction in the EPI-SOD multicenter trial. *Am J Gastroenterol*. 2014;109(3):436-442.

Cotton PB, Durkalski V, Romagnuolo J, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. *JAMA*. 2014;311(20):2101-2109.

Freeman ML, Gill M, Overby C, Cen YY. Predictors of outcomes after biliary and pancreatic sphincterotomy for sphincter of oddi dysfunction. *J Clin Gastroenterol*. 2007;41(1):94-102.

Petersen BT. An evidence-based review of sphincter of Oddi dysfunction: part I, presentations with "objective" biliary findings (types I and II). *Gastrointest Endosc*. 2004;59(4):525-534.

Petersen BT. Sphincter of Oddi dysfunction, part 2: evidence-based review of the presentations, with "objective" pancreatic findings (types I and II) and of presumptive type III. *Gastrointest Endosc*. 2004;59(6):670-687.

Romagnuolo J, Cotton PB, Durkalski V, et al. Can patient and pain characteristics predict manometric sphincter of Oddi dysfunction in patients with clinically suspected sphincter of Oddi dysfunction? *Gastrointest Endosc*. 2014;79(5):765-772.