

Post-cholecystectomy pain; a clinical minefield

SEEKING PATIENTS FOR AN NIH-FUNDED RESEARCH STUDY IN SPHINCTER OF ODDI DYSFUNCTION

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The diagnosis of Sphincter of Oddi Dysfunction (SOD) is often considered in patients with recurrent pain after cholecystectomy. Many of them have impressive objective findings on laboratory studies or imaging (e.g. abnormal liver enzymes, or a dilated bile duct), and are categorized by the Milwaukee classification as SOD Type I^{1, 2}. Most of these are found at ERCP to have small bile duct stones or fibrotic sphincter stenosis, and are treated (usually effectively) by endoscopic biliary sphincterotomy.

Much more problematic are the many patients who have only minimal findings, such as a slightly "dilated" duct, or elevated transaminases (i.e. SOD Type II), or no objective abnormalities at all (i.e. Type III). These Type III patients in particular are very difficult to evaluate and manage¹⁻³. ERCP is known to carry substantial risks in this context⁴. Empiric sphincterotomy is speculative at best, and dangerous at worst. Even if disasters do not occur, many patients find themselves on a slippery slope of repeated unhelpful procedures and some eventually undergo major surgeries.

The challenge is to define which patients (if any) with "SOD Type III" really do have sphincter dysfunction, and may benefit from sphincter ablation. Some physicians are skeptical of the very existence of SOD, or assume that it is a psychiatric issue, or only a small part of a broader problem of motility disturbance

or visceral hypersensitivity. The categorization problem has been helped recently with the publication of the ROME III criteria⁵. SOD and other digestive dysfunctions are clearly defined on clinical grounds (certain patterns of pain and disability) in the absence of detectable structural disease.

Endoscopic ultrasound and MRCP (preferably with secretin infusion) are helpful in excluding pathology, and should be considered before embarking on ERCP. Non-invasive tests of sphincter activity, such as morphine-prostigmine provocation and dynamic isotope studies, have not found general favor. Trials of medical therapy, such as anti-depressants and calcium channel blocking agents, are rarely effective in the long term¹.

Sphincter of Oddi Manometry (SOM) is widely considered to be the "gold standard" for the diagnosis of SOD, but the evidence is wafer thin. Cohort studies of manometry-directed sphincterotomy claim improvement in only about two thirds of patients^{1, 2}. There is no data as of yet to support the predictive value of manometry in Type III patients.

The EPISOD study (Evaluating Predictors of Interventions in Sphincter of Oddi Dysfunction) is funded by NIDDK



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and has been designed to answer the key questions:

1. Are there patients with SOD Type III that respond to sphincterotomy?
2. If so, which characteristics predict the outcome?
 - a. Reasons for the cholecystectomy, and initial response to it
 - b. Pain patterns
 - c. Psychological profiles
 - d. Presence or absence of other functional GI disorders
 - e. Results of sphincter manometry (SOM)

The main eligibility criteria for the study are:

- Age 18-65
- Disabling biliary-type pain (fitting Rome III criteria)
- Cholecystectomy > 3 months ago
- Negative CT or MRCP with bile duct 9mm or less
- EGD with no relevant pathology, negative HP testing, or prior treatment
- Bilirubin, alk phos, lipase, amylase all <2XULN; AST and ALT <3XULN
- Pain persistent despite treatment with PPI, and trial of anti-spasmodics
- No daily narcotics
- No prior sphincterotomy or biliary diversion surgery
- No major psyche issues
- No prior pancreatitis

After informed consent, subjects undergo ERCP with biliary and pancreatic manometry. They are then randomized to sphincterotomy or sham (2:1 ratio), regardless of the manometry results. Those randomized to the sphincterotomy arm and have raised pancreatic sphincter pressures are randomized again to biliary or to biliary and pancreatic sphincterotomy. All subjects get a small temporary pancreatic stent. Subjects are referred back for ongoing care,

but followed by phone by research coordinators for a year. Further standard treatment can be given if progress is not satisfactory. Patients, caregivers and research coordinators are blinded to the treatment allocation. Success is defined by substantial reduction in pain burden at one year (without any repeat intervention). The grant pays for the initial ERCP procedure.

While some patients are nervous about getting "sham treatment," their chance of getting a sphincterotomy (2:1) is the same or better than standard therapy which dictates sphincterotomy only for abnormal manometry, which is found in less than two thirds of these patients.

There are eight study centers in the USA:

1. Medical University of South Carolina, Charleston, SC (PI J. Romagnuolo)

2. Indiana University, Indianapolis, IN (E. Fogel)
3. University of Alabama, Birmingham, AL (M. Wilcox)
4. Johns Hopkins University, Baltimore, MD (A. Kalloo)
5. Methodist Dallas Medical Center, Dallas, TX (P. Tarnasky)
6. Midwest Therapeutic Endoscopy Consultants, St. Louis, MO (G. Aliperti)
7. University of Minnesota, Minneapolis, MN (M. Freeman)
8. Virginia Mason Medical Center, Seattle, WA (R. Kozarek)

Contact details are available from www.clinicaltrials.gov or Kyle Orrell (843) 876-4303, or email: orrell@musc.edu.

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Dr. Peter Cotton is Medical Director of the Digestive Disease Center, Professor of Medicine, and Assistant Dean for International Activities at the Medical University of South Carolina in Charleston. He attended Cambridge University and St. Thomas Hospital Medical School (London), where he developed the Endoscopy Laboratory at St. Thomas' Hospital while still officially in training. Dr. Cotton left England to become Professor of Medicine and Chief of Endoscopy at Duke University, Durham, North Carolina, and developed a state of the art endoscopy center. He moved to Charleston, South Carolina in 1994 to initiate the Digestive Disease Center. Dr. Cotton has been active in many national and international organizations, and has given invited lectures and demonstrations in 47 countries. He was awarded the Rudolph Schindler award of the American Society for Gastrointestinal Endoscopy in 2004. He can be reached at (843) 876-7226 or cottonp@musc.edu.

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