



Sphincter of Oddi dysfunction: Managing the patient with chronic biliary pain

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Abstract

Sphincter of Oddi dysfunction (SOD) is a syndrome of chronic biliary pain or recurrent pancreatitis due to functional obstruction of pancreaticobiliary flow at the level of the sphincter of Oddi. The Milwaukee classification stratifies patients according to their clinical picture based on elevated liver enzymes, dilated common bile duct and presence of abdominal pain. Type I patients have pain as well as abnormal liver enzymes and a dilated common bile duct. Type II SOD consists of pain and only one objective finding, and Type III consists of biliary pain only. This classification is useful to guide diagnosis and management of sphincter of Oddi dysfunction. The current gold standard for diagnosis is manometry to detect elevated sphincter pressure, which correlates with outcome to sphincterotomy. However, manometry is not widely available and is an invasive procedure with a risk of pancreatitis. Non-invasive testing methods, including fatty meal ultrasonography and scintigraphy, have shown limited correlation with manometric findings but may be useful in predicting outcome to sphincterotomy. Endoscopic injection of botulinum toxin appears to predict subsequent outcome to sphincterotomy, and could be useful in selection of patients for therapy, especially in the setting where manometry is unavailable.

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Key words: Sphincter of Oddi dysfunction; Manometry; Review

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INTRODUCTION

Sphincter of Oddi dysfunction (SOD) is characterized by symptoms of pancreaticobiliary obstruction in the absence of other structural causes. Symptoms attributable to SOD can be seen in three clinical scenarios: (1) the post-cholecystectomy syndrome; (2) acalculous biliary pain with an intact gallbladder; and (3) recurrent idiopathic pancreatitis. Its prevalence in the general population is 1.5%^[1]. SOD is seen in 1% of patients after cholecystectomy, but in 14%-23% of patients with the post-cholecystectomy syndrome (biliary pain with elevated liver enzymes)^[2,3]. This may reflect either disclosure of SO dysfunction after the reservoir function of the gallbladder is removed or that the symptoms leading to cholecystectomy are in fact caused by SO dysfunction. SOD can also be detected in 29% of patients with unexplained right upper quadrant pain and no evidence of gallstone disease^[4], although due to symptom overlap many of these patients are not detected until after cholecystectomy. The prevalence of SOD in recurrent "idiopathic" pancreatitis ranges from 14.7%-72%^[5-7]. A high index of suspicion is required to make the diagnosis after ruling out structural causes. Diagnosis is further limited by the wide spectrum of presentations (from predominantly structural SO stenosis to predominantly functional SO dyskinesia), as well as by the limited availability of invasive diagnostic techniques, such as manometry. We present herein a review of the literature and propose an approach to management of the SOD patient specifically in the setting where manometry is unavailable.

CLINICAL MANIFESTATIONS

Although SOD can be seen in any age group or gender, it is most commonly seen in women between the ages of 20 and 50 years^[1]. Patients with predominantly biliary symptoms present with pain localized to the right upper quadrant or epigastrium lasting 30 min or more and should meet the Rome II diagnostic criteria for biliary-type pain^[8]. To meet these criteria, the patients must have episodes of severe, steady pain in the epigastrium and right upper quadrant as well as all of: (1) episodes lasting 30 min or more; (2) symptoms occurring on one or more occasions in the previous 12 mo; (3) steady pain that interrupts daily activities or requires consultation with a

physician; and (4) no evidence of structural abnormalities to explain the symptoms. These patients may also have associated elevated conjugated bilirubin, transaminases or alkaline phosphatase, particularly during episodes of pain. A clinical classification system popularized by Geenen and Hogan separates patients with suspected biliary SOD into three groups based on the presence of objective signs of biliary obstruction^[9]. Type I SOD is characterized by biliary pain as well as elevated liver enzymes (alkaline phosphatase and AST more than twice normal) on at least two separate occasions, a dilated common bile duct (> 12 mm at ERCP), and delayed contrast drainage from the bile duct (more than 45 min). Type II SOD is characterized by biliary pain and only one or two of the aforementioned objective criteria, and Type III SOD presents with only biliary pain and no objective criteria. This classification system has subsequently been modified by eliminating the delayed contrast drainage criterion as it is both cumbersome and often unreliable.

Type I patients are thought to have sphincter of Oddi stenosis as a cause for their symptoms and are likely to respond to endoscopic sphincterotomy. Type III patients represent a group of patients with true functional pain who may have sphincter of Oddi dyskinesia either alone or as part of a more diffuse smooth muscle dysmotility disorder. Type II patients represent an overlap between structural SO obstruction and a motility disorder, and the etiology can often be clarified by manometry. This clinical classification system also correlates with manometric findings, with elevated basal sphincter of Oddi pressures in 60%-85% of Type I, 18%-55% of Type II and 7%-28% of Type III patients^[3,10].

When the pancreatic sphincter is involved, SOD can present with acute pancreatitis and should be considered in the differential diagnosis of recurrent idiopathic pancreatitis. A set of clinical criteria similar to those used to stratify biliary-type SOD has been utilized for pancreatic-type SOD^[10]. Type I consists of recurrent pancreatitis and/or typical pancreatic pain and all of (1) elevated lipase or amylase more than one and a half times normal, (2) dilated pancreatic duct (head > 6 mm, body > 5 mm), and (3) prolonged pancreatic drainage time (> 9 min). Type II consists of typical pancreatic pain and only one or two of the other criteria, and Type III consists of typical pancreatic pain only. As in biliary pain patients, the clinical classification correlates with the likelihood of manometric abnormality with elevated basal pancreatic sphincter pressures in 92% of Type I, 58% of Type II and 35% of Type III patients^[10].

PATHOGENESIS

The sphincter of Oddi is a smooth muscle sphincter which impedes biliary flow when contracted. It is composed of three sphincteric regions. First is the biliary sphincter, which is 10 mm long and controls biliary flow from the common bile duct. The pancreatic sphincter is slightly shorter (6 mm) and controls flow of secretions through the pancreatic duct. Finally, a 6-mm long common sphincter encircles the confluence of the pancreatic and bile ducts as they near the duodenal lumen^[11]. A component of the sphincter is intraluminal, and it is this portion that

is transected during endoscopic sphincterotomy. The etiology of SOD is not entirely clear. Pain is presumed to be due to obstructed biliary or pancreatic flow leading to increased upstream pressure. This is especially evident in the post-cholecystectomy population where removal of the gallbladder may eliminate a reservoir for backflow of bile. Elevated sphincter pressure has also been shown to produce acute pancreatitis in an animal model^[12]. In some patients, there may be fixed obstruction at the level of the papilla. Biopsies of the ampullary region show inflammation or fibrosis in 43% of patients with SOD^[13]. These patients may correspond to Type I SOD with a fixed "papillary stenosis" picture.

Microlithiasis has been proposed as a possible contributing factor by creating a transient obstruction. However, only 3.5%-5% of patients with symptoms of SOD have microlithiasis detected in bile samples^[14,15]. In addition, there is no difference in the frequency of microlithiasis between symptomatic patients with elevated sphincter pressures and those with normal manometry^[14,15], so microlithiasis is not likely to explain symptoms in these patients. Another potential cause for SOD symptoms is a motor abnormality of the sphincter of Oddi, or "biliary dyskinesia". In addition to elevated resting basal sphincter pressures, SOD has been associated with increased frequency of phasic contractions, increased retrograde propagation of contractions and a paradoxical response to cholecystokinin (CCK)^[16]. A paradoxical response to CCK (failure to completely obliterate phasic contractions) is seen more frequently in SOD patients with concomitant irritable bowel syndrome, indicating the possibility of a global gut motility disorder^[17]. Supporting this theory is the presence of increased phase II and III migrating motor complex activity in the small bowel of post-cholecystectomy patients with objective evidence of SOD^[18].

SOD patients also exhibit increased non-gastrointestinal symptomatic complaints and increased rates of childhood sexual abuse compared to controls^[19], similar to that seen in irritable bowel syndrome. In one series, a formal diagnosis of somatization disorder was made in 30% of women with SOD and none of controls. In patients with Type III SOD (those with no objective signs of biliary obstruction), increased rates of depression, obsessive compulsive traits and anxiety compared to controls are also seen^[20]. Visceral hyperalgesia is postulated to cause pain in irritable bowel syndrome, and indeed duodenal hyperalgesia as assessed with duodenal barostat was confirmed in SOD Type III when compared to controls^[20]. Interestingly, no evidence of rectal hyperalgesia was detected in Type III SOD patients compared to controls^[20], while irritable bowel patients had significantly lower rectal pain thresholds compared to SOD patients and controls^[21]. Thus, at least in Type III SOD, visceral hyperalgesia and psychiatric factors may play a role in symptoms, necessitating a multidisciplinary approach to pain control.

DIAGNOSIS

Diagnostic evaluation in patients with pancreaticobiliary

symptoms should begin by ruling out structural causes for pain. Liver biochemistry as well as pancreatic enzymes should be drawn. Radiologic imaging is somewhat site-dependent but may include transabdominal ultrasound, endoscopic ultrasound, CT scan, MRCP, ERCP and analysis of bile for crystals. Up to 4.3% of patients with suspected SOD may have an ampullary tumor as the cause of their symptoms, so biopsies of the ampullary region should be considered^[13]. When no other explanation for a patient's symptoms can be found, a variety of diagnostic methods exist to confirm the diagnosis of SOD.

Manometry

Manometry is the accepted gold standard for diagnosis of SOD since symptoms are thought to stem from obstructed biliary or pancreatic flow at the level of the sphincter of Oddi. Manometry findings have been shown to be reproducible^[22] with good interobserver variability^[23]. Geenen *et al*^[24] found manometric findings were stable over time when repeated. However, these results were recently refuted in a group of patients with normal manometry and persistent symptoms^[25]. Repeat manometry in this group of 12 patients diagnosed SOD in five patients with eventual symptom relief after endoscopic therapy. In the absence of a pathologic gold standard for comparison, most studies have used elevated basal sphincter pressure when compared to duodenal pressure as diagnostic of SOD^[24,26]. An elevated basal sphincter pressure is defined as > 40 mmHg (3 SD greater than that of healthy volunteers)^[27]. This SO hypertension is deemed likely to correlate with SO obstruction, and indeed most studies have found a correlation between SO hypertension on manometry and outcome after endoscopic sphincterotomy^[24,28-30]. Other motility abnormalities include increased frequency of phasic contractions (> 8/min), increased retrograde propagation of phasic contractions (> 50%), and paradoxical response to cholecystokinin^[16], although these findings of "SO dysmotility" have generally not been used to select patients in outcome studies. In fact, the one study that did compare outcome after sphincterotomy in patients with SO hypertension and those with other markers of dysmotility found no difference in outcome between patients with normal manometry and those with SO dysmotility, whereas patients with elevated basal sphincter pressures had a significant benefit after sphincterotomy^[31]. Thus, although sphincter dysmotility may be seen in patients with SOD symptoms, it is not successfully treated with sphincterotomy, possibly because it causes pain through mechanisms other than obstruction to biliary flow.

When SO manometry is performed for presumed SOD, it is now generally accepted practice to measure pressures at both the biliary and pancreatic sphincter. Discordant results are obtained from the pancreatic and biliary sphincters in 30%-48% of patients^[6,32,33], indicating that manometry should be performed at both sphincters so as not to misdiagnose patients who could ultimately benefit from therapy. Manometry is limited by its availability and the level of technical expertise required for its performance. One must be cautious that the drugs used for sedation do not alter SO motility, as midazolam has

been found to reduce basal SO pressure^[34] and narcotics to cause SO spasm^[35]. Diazepam does not appear to have an effect on SO motility and may be safely used as sedation in this setting^[36]. Manometry is also an invasive diagnostic procedure with a potential risk of pancreatitis in 17%-27% of cases^[37,38]. Much of the risk of pancreatitis seen after manometry appears to be attributable to concomitant ERCP as a significantly lower rate of pancreatitis is seen in patients who undergo manometry alone compared to manometry with ERCP (9.3% *vs* 26.1%)^[37], and there is no significant difference in pancreatitis rates between SOD patients undergoing ERCP alone compared to ERCP plus manometry (OR = 0.72)^[38]. However, the 9% pancreatitis risk seen in patients who underwent SO manometry alone is still a significant adverse outcome that must be weighed against the benefits of this diagnostic modality.

Finally, although manometry has been shown to correlate with endoscopic outcome in many studies as previously mentioned, it is not 100% sensitive. In a study by Rolny *et al*^[39], 35% of Type I SOD patients had normal manometry but still benefited from endoscopic sphincterotomy. Similarly, in a study by Wehrmann *et al*^[40], manometry findings were similar between Type II and Type III SOD patients, but therapeutic response was significantly better in patients with Type II SOD. Because of the imperfect predictive value of manometry as well as its limited availability and potential for adverse effects, much attention has been paid to non-invasive diagnostic techniques.

Quantitative hepatobiliary scintigraphy

Hepatobiliary scintigraphy (HBS) is performed in the fasting state and involves administration of a radionuclide tracer to quantitate biliary flow. In the setting of SOD, obstructed biliary flow is expected which can be quantitated using a number of outcome measures. Intravenous CCK infusion is used to enhance bile flow and aid in the demonstration of obstruction. Although an attractive alternative to manometry due to its non-invasive nature, studies of HBS have been limited by the lack of a standardized protocol and the use of a variety of outcome measures [duodenal appearance time (DAT), hilum-to-duodenum transit time (HDTT), or a composite scintigraphic score]. The variability in study protocol may in part explain the wide range of reported sensitivities (from 25 to 100%) and specificities (from 78% to 100%)^[41-43].

An early study by Sostre *et al*^[43] reported a sensitivity and specificity of 100% for the diagnosis of SOD using a scintigraphic score composed of (1) time to peak liver activity, (2) time of first visualization of the intrahepatic biliary tree, (3) biliary tree prominence, (4) time of visualization of bowel, (5) percent common bile duct emptying, and (6) CBD to liver ratio. However, these results were from a small series of twelve patients, and only seven of these patients had elevated basal sphincter pressure. These impressive results have not been replicated to date.

Using HDTT, DAT and half time of excretion as outcomes, Madacsy *et al*^[44] found a significant difference in scintigraphic parameters between SOD patients with elevated sphincter pressures and asymptomatic controls.

They found HDTT to be the most sensitive measure with a sensitivity of 89%. However, this was a small study with twenty controls and twenty patients, of whom only nine had elevated basal sphincter pressures. Subsequently, a study of 29 patients with persistent post-cholecystectomy pain undergoing both manometry and scintigraphy showed a sensitivity of only 25%-38% and specificity of 86%-89% when using various cut-off values for the previously described scintigraphic score^[41]. The sensitivity of HDTT was equally poor at 13%, although the specificity was 95%. No correlation was found between basal SO pressure and HDTT value. Similarly, a prospective series of 304 patients with suspected SOD compared HBS to manometry as the gold standard. Sensitivity and specificity were 49% and 78%, respectively, using hepatic peak, half time and percent CBD clearance as outcome measures^[42]. These larger, prospective studies using manometry as a gold standard showed that HBS is not sensitive or specific compared to manometry as a diagnostic modality.

Interobserver variability and reproducibility of the scintigraphic score was examined in a group of asymptomatic post-cholecystectomy patients with normal liver enzymes^[43]. Interobserver agreement was good ($\kappa = 0.507$), but when two scans for each patient were compared there was poor agreement ($\kappa = 0.062$), indicating poor reproducibility. Interestingly, in this asymptomatic population, 40% had at least one of their two HBS studies reported as abnormal, indicating a significantly lower specificity than previously reported for this score. Although correlation between HBS and manometry seems to be poor, one must remember that manometry is not a perfect gold standard. The most important outcome to be considered is response to therapy, and it is possible that a functional test of bile flow may detect patients with normal manometry who may nonetheless respond to endoscopic sphincterotomy. This was demonstrated by Cicala *et al*^[44] in a group of Type I and Type II SOD patients where prolonged HDTT predicted a response to endoscopic therapy in 93% of cases, as compared to only 57% of responses predicted by manometry. In this study, all Type I patients had abnormal scintigraphy studies, as did 64% of Type II patients, and all patients with abnormal manometry also had abnormal HBS. In a different study which showed a poor correlation between HBS and manometry, HBS predicted 86% of patients who subsequently had a long-term symptomatic response to sphincterotomy^[42]. Thus, although the role of HBS in diagnosing SOD remains undetermined, it may have a place in predicting therapeutic outcomes and determining which patients should undergo endoscopic sphincterotomy. Variations on the HBS technique may also improve its diagnostic ability. Morphine provocation to accentuate sphincter of Oddi spasm during HBS produced a significantly different percent excretion of tracer between patients with normal and abnormal SO motility^[47]. Sensitivity was 83% and specificity 81% for this technique compared to manometry as a gold standard. A functional obstruction in SOD patients was demonstrated by the administration of glyceryl trinitrate which reversed the abnormal HBS findings in a group of patients with abnormal SO manometry, while having no effect on patients with mechanical biliary obstruction^[48]. It

is possible that further refinement of these techniques may aid in diagnosis of SOD and prediction of outcome to therapy, but further trials with response to sphincterotomy as an outcome are needed.

Fatty meal ultrasonography

Fatty meal ultrasonography (FMU) is performed by ingestion of a standardized fatty meal with ultrasound performed before and 45 min after ingestion. The fatty meal stimulates release of CCK which induces bile flow. In the setting of a functional obstruction to bile flow, this causes dilation of the diameter of the common bile duct when compared to baseline. Sensitivity of FMU when compared to manometry in SOD patients is only 21%, although specificity is 97%^[42]. Similar to HBS, however, 87% of patients with abnormal FMU results did have a therapeutic response to sphincterotomy, indicating a possible role in selection of patients for therapy. The utility of both FMU and HBS for diagnosis is further limited because their accuracy falls as objective signs of SOD decrease. Ninety percent of SOD Type I patients had abnormal findings in at least one of these non-invasive tests, as compared to only 50% with Type II and 44% with Type III SOD^[42]. Type I patients have more objective signs of biliary obstruction and pose less of a diagnostic dilemma than Type II and III patients who are the patients who would most benefit from a non-invasive diagnostic test prior to contemplating invasive therapy such as sphincterotomy. This limitation further restricts the use of non-invasive diagnostic testing at this time.

Non-invasive testing of the pancreatic sphincter

Fatty meal ultrasonography and hepatobiliary scintigraphy assess bile flow, but SOD can also present with pancreatitis due to a hypertensive pancreatic sphincter. Non-invasive testing of the pancreatic portion of the sphincter of Oddi has centered on the use of secretin to stimulate pancreatic flow with subsequent assessment of pancreatic ductal dilatation as a marker of obstructed flow. The secretin test was initially performed with trans-abdominal ultrasound, and was found to have a sensitivity of 88% and a specificity of 82% when compared to manometry in patients with recurrent idiopathic pancreatitis^[49]. Not surprisingly, concordance with results from pancreatic manometry was superior to concordance with manometry findings from the biliary sphincter. An endoscopic ultrasound-guided secretin test has also been described^[50]. A lower sensitivity of only 57% and specificity of 92% were reported with this technique, although only 20 patients with SOD were examined. Again, the secretin test was less accurate in detecting a hypertensive biliary sphincter as compared to pancreatic sphincter hypertension. A preliminary study of secretin MRCP in 15 patients with recurrent idiopathic pancreatitis showed concordance in 13 (87%) of these patients^[51]. The two patients in whom MRCP results were false negatives were patients with normal basal sphincter pressures but some other form of sphincter dysmotility. These results are intriguing, and MRCP could have the added benefit of ruling out structural causes of pancreaticobiliary symptoms in these patients, reducing the need for invasive testing, such as ERCP and SO

manometry, in this high-risk group of patients. Further evidence of the utility of secretin MRCP is necessary at this time.

THERAPY

Medical therapy

Medical therapy for SOD has been disappointing. Calcium channel blockers, such as nifedipine, have been shown to decrease sphincter of Oddi pressure in healthy subjects^[52]. In small placebo-controlled, crossover studies, nifedipine also decreased biliary-type pain in patients with Type II sphincter of Oddi dysfunction^[53,54], however, these trials were of short duration (twelve to sixteen weeks of active treatment). A more recent attempt at a longer duration of nifedipine therapy for sphincter of Oddi dysfunction (types II and III) was terminated due to unacceptably high rates of side effects, including peripheral edema, headache and dizziness^[55] and did not show a reduction in pain episodes compared to placebo. The effect of nitrates on the sphincter of Oddi has also been investigated. Oral nitrates have been shown to reduce sphincter of Oddi pressure^[56,57] but no clinical trials have assessed their use in SOD, and therapy is likely to be limited by side effects, such as headache. Overall, medical therapy to date has been limited by medication side effects, the inconvenience of long-term oral therapy, and the possibility of tachyphylaxis, and is not currently standard of care for sphincter of Oddi dysfunction. Other avenues of potential medical treatment remain to be explored. Intravenous octreotide effectively decreases basal and peak sphincter pressures in SOD patients when compared to a placebo infusion^[58]. Clinical trials to determine whether this effect translates into improved clinical endpoints would be beneficial, especially with the availability of a long-acting injectable form of octreotide. Preliminary data with the prostaglandin E1 analogue, alprostadil alfadex, as well as the protease inhibitor, gabexate mesilate showed relaxant effects on the sphincter of Oddi^[59,60], and their clinical utility also remains to be explored. One small study showed a relaxant effect on sphincter of Oddi motility with the use of electroacupuncture at an acupoint thought to be related to the hepatobiliary system when compared to a control acupoint^[61]. A reduction in basal sphincter pressure as well as phasic contraction was seen during electroacupuncture, which was associated with elevation of plasma CCK levels. It remains to be seen whether this novel therapy could present a non-invasive therapeutic option for SOD.

Endoscopic therapy

Since the clinical symptoms of sphincter of Oddi dysfunction are thought to stem from a functional obstruction at the level of the sphincter, sphincterotomy to alleviate this obstruction would seem a promising therapeutic avenue. This is especially true in Type I SOD, where objective features of biliary obstruction (elevated liver enzymes and a dilated common bile duct) are present. Indeed, Rolny *et al*^[39] treated a group of seventeen Type I SOD patients with sphincterotomy and found that despite the fact that sphincter of Oddi hypertension was not found in 35% of

patients at manometry, all patients experienced pain relief after sphincterotomy for a mean follow-up of 28 mo (Table 1). These results were replicated in a series reported by Sugawa *et al*^[62], in which Type I SOD patients underwent sphincterotomy without prior manometry. All patients in this series experienced symptom resolution at 26 mo of follow-up^[62]. Based on these outcomes, sphincterotomy is recommended in Type I patients without prior manometry, since these patients are likely to have a clinical improvement regardless of manometric findings.

Type II and III patients have fewer clinical manifestations of high grade biliary obstruction, and correspondingly are less likely to respond to endoscopic sphincterotomy (Table 1). In a landmark trial by Geenen *et al*^[24], 47 Type II SOD patients were randomized to sphincterotomy or sham. Manometry was also performed. For patients with elevated sphincter of Oddi pressure, 10 of 11 patients who underwent sphincterotomy had improvement in pain scores at one year, as compared to only 3 of 12 patients who underwent sham. This benefit was also seen when follow-up was extended to four years, with a 94% clinical response rate after sphincterotomy in patients with elevated basal sphincter pressures as compared to clinical improvement in one third of patients with normal baseline pressures regardless of treatment. Since patients with normal manometry had no difference in pain relief between the sphincterotomy and sham groups, SO manometry is recommended in Type II SOD patients prior to subjecting them to the possible adverse effects of a sphincterotomy. Subsequent studies have both confirmed the efficacy of sphincterotomy for patients with elevated basal pressures and shown no response in patients with normal pressures or with sphincter dyskinesia^[28-31]. Sphincterotomy is then recommended only in Type II patients with elevated basal sphincter pressures.

Subsequent studies of endoscopic therapy have included patients with Type III SOD, who have no objective findings of biliary obstruction. A retrospective analysis showed no difference in baseline sphincter hypertension between Type II and Type III patients (60% *vs* 55%, respectively), and subsequently showed no difference in the proportion of Type II and Type III patients in response to sphincterotomy (68% *vs* 56%, respectively)^[63]. A prospective trial by Wehrmann *et al*^[40] confirmed that a similar proportion of Type II and Type III patients had manometric findings of SOD, but found that only 8% of Type III patients had a sustained clinical improvement at 2.5 years of follow-up, as compared to 60% of Type II patients. Based on these findings, manometry in Type III SOD patients should be approached with caution as it both carries procedural risks and does not reliably predict outcome to sphincterotomy.

Risks of sphincterotomy

Sphincter of Oddi manometry is limited by its availability as well as potential complications of the procedure. Indeed, SOD has been shown to carry an increased risk of post-ERCP pancreatitis with frequencies ranging from 12.5% to 27%^[38,64,65] as compared to 3%-5% of patients who undergo ERCP for bile duct stones. In patients with

Table 1 Sphincter of Oddi dysfunction: Outcome after sphincterotomy

Author, yr	n	Milwaukee Class	Response rate (%)	Duration (mo)	Pancreatitis (%)
Neoptolemos ^[29] 1988	30	NS	19/30 (63%) Manometry in 23 patients: Man + ve 15/18 (83%) Man - ve 0/5 (0%)	46	4/30 (13%)
Rolny ^[39] 1993	17	Type I	17/17 (100%)	28	NS ¹
Sugawa ^[62] 2001	8	Type I	8/8 (100%)	26	0
Geenen ^[24] 1989	23 sphincterotomy (24 sham Rx)	Type II	15/23 (65%) Man + ve ² 10/11 (91%) Man - ve ² 5/12 (42%)	12	2/47 (4%)
Toouli ^[31] 2000	37 sphincterotomy (42 sham Rx) (2 excluded)	Type I (9) Type II (72)	11/13 (85%) man+ve ² 12/24 (50%) man-ve ²	24	7/81 (9%)
Fullarton ^[28] 1992	10	Type II	8/10 (80%) all man+ve ²	24	NS ¹
Lin ^[72] 1998	24	Type II	19/24 (79%) Enzyme+ve 18/20 (90%) Enzyme-ve 1/4 (25%)	18	2/24 (8%)
Botoman ^[63] 1994	43	Type II (21) Type III (22) man+ve	Type II 14/21 (67%) Type III 12/22 (55%)	37	Type II 16% Type III 15%
Bozkurt ^[30] 1996	23	Type II and III	19/23 (83%) man+ve ²	8-62	NS ¹
Wehrmann ^[40] 1996	37 (with + ve manometry)	Type II (22) Type III (15)	Type II 13/22 (60%) Type III 1/15 (8%)	30	NS ¹

¹NS= not specified; ²Man+ve = manometry positive; Man-ve = manometry negative.

SOD, manometry does not appear to independently increase the risk of pancreatitis, but pancreatitis is increased with biliary sphincterotomy (OR = 5.13) and pancreatography (OR = 11.32)^[38]. Since pancreatitis in this setting is thought to result from edema at the level of the sphincter of Oddi, trials of pancreatic stents to improve pancreatic drainage have been performed. Although an early study did not show a significant benefit for pancreatic stenting^[66], subsequent trials have shown a significant reduction in pancreatitis in patients who have a pancreatic stent placed at the time of biliary sphincterotomy^[67-69]. A subsequent meta-analysis confirms the benefit of pancreatic stenting to decrease pancreatitis in high-risk patients (including sphincter of Oddi dysfunction) with an odds ratio of 0.3 and a number needed to treat of eleven^[70]. Preliminary evidence with botulinum toxin injection into the pancreatic sphincter to prevent pancreatitis after biliary sphincterotomy shows a trend towards benefit. Six of fourteen (43%) patients in the sham arm developed pancreatitis compared to three of twelve (25%) patients in the botulinum toxin arm^[71]. Until more trials with botulinum toxin become available, the use of prophylactic pancreatic duct stenting in these high risk patients should be strongly considered, especially if additional risk factors such as a small common bile duct are present.

Selecting patients for sphincterotomy

Because of the problems of availability and adverse effects, non-invasive surrogate markers predicting outcome after sphincterotomy have been sought with conflicting results. Retrospective analysis has shown a better outcome

after sphincterotomy in patients with greater common bile duct diameter or delayed contrast drainage from the bile duct^[29]. Another retrospective series of Type II SOD patients did not find common bile duct diameter to be predictive of outcome after sphincterotomy, but did find elevated liver enzymes to predict clinical resolution after endoscopic therapy^[72]. Patients in this series did not have SOD confirmed by manometry, and some of the response after sphincterotomy may have been due to microlithiasis, which would also have caused elevated liver enzymes. However, in prospective studies, none of elevated liver enzymes, common bile duct diameter, common bile duct drainage or a morphine-prostigmine test predicted outcome after sphincterotomy^[24,31].

Quantitative choledochoscintigraphy has been compared to manometry as a predictor of outcome after sphincterotomy. Scintigraphy has the advantage of providing functional information regarding bile flow, as opposed to the structural information provided by manometry. Scintigraphy showed a prolonged hepatic hilum-duodenum transit time (HHDT) in all eight Type I SOD patients studied as well as 64% of Type II SOD patients. HHDT was abnormal in all of the patients with abnormal manometry as well as 46.66% (7/15) patients with normal SO pressure^[46]. In 14 patients who subsequently underwent sphincterotomy, symptomatic improvement was accurately predicted by scintigraphy in 13 (93%), while manometry predicted improvement in only eight (57%). Scintigraphy is thus a promising non-invasive method for prediction of outcome after sphincterotomy, even in patients with normal manometry who may have a functional obstruction to

bile flow causing their biliary-type pain. Larger studies are needed to confirm these findings.

Biliary stenting may predict outcome after sphincter ablation. In a small prospective series, 90% of patients who had a symptomatic response 12-14 wk after placement of a biliary stent subsequently responded to sphincterotomy^[73]. The stent trial had a positive result in all of the 7 patients with elevated sphincter of Oddi pressure (6 of whom later responded to sphincterotomy) as well as in 16 patients with normal manometry (of whom 5 subsequently responded to sphincterotomy). Although a biliary stent trial may detect some patients with normal manometry who may subsequently benefit from sphincter ablation, it requires a second invasive procedure to be performed in a significant proportion of patients who do not benefit, and thus is not a viable option to select patients for sphincterotomy. In the absence of reproducible non-invasive predictors of response to sphincterotomy, some have suggested performing empirical sphincterotomy in Type II SOD without prior manometry^[74]. Manometry-guided therapy was compared to empiric sphincterotomy with a decision analysis model, and the empiric sphincterotomy pathway was shown to cut costs from \$2790 per patient to \$2244 per patient. Fifty-five percent of the manometry-guided group was predicted to experience symptom resolution, as compared to 60% in the empiric sphincterotomy group. Randomized, controlled trials to compare these two treatment options are necessary, but in centres where manometry is unavailable, empiric sphincterotomy may be justifiable.

Botulinum toxin

Botulinum toxin acts by inhibiting presynaptic release of acetylcholine to inhibit contraction in smooth and striated muscle. Because of this property, it has been used for a variety of gastrointestinal disorders characterized by elevated muscle tone, including achalasia, gastroparesis and anal fissure^[75]. Botulinum toxin has been shown to reduce sphincter of Oddi pressure in animals^[76], and subsequently in case reports in patients with SOD^[77,78]. Two uncontrolled case series have examined the clinical effect of botulinum toxin for both biliary type SOD^[79] and for recurrent pancreatitis due to pancreatic SOD^[80]. In patients with biliary type pain (type III SOD), endoscopic sphincterotomy is of uncertain benefit^[40], and given the high risk of pancreatitis^[64] in patients with SOD, a less invasive option such as botulinum toxin injection is attractive. Of 22 type III SOD patients treated with 100-unit botulinum toxin injection, 12 had a resolution of symptoms^[79]. Eleven of these patients underwent endoscopic sphincterotomy when they developed recurrent pain, and all of these patients responded to sphincterotomy. In contrast, none of the botulinum toxin non-responders experienced symptom resolution after sphincterotomy despite a significant reduction in sphincter of Oddi pressure, indicating that a hypertensive sphincter of Oddi was not the cause of their abdominal pain. A trial of botox injection had a positive predictive value of 100% and a negative predictive value of 80% in predicting the outcome of sphincterotomy, illustrating the potential utility of using botulinum toxin injection as a diagnostic and

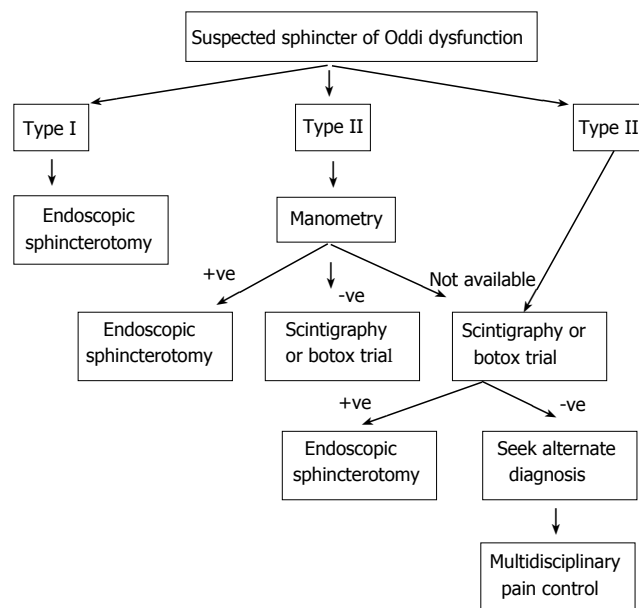


Figure 1 Sphincter of Oddi Dysfunction: Management algorithm.

therapeutic trial before proceeding to the more invasive procedure of sphincterotomy. Similarly, in patients with recurrent pancreatitis and elevated pancreatic sphincter of Oddi pressures, 80% (12/15) patients had no further pancreatitis attacks for a mean of six months after botulinum toxin injection^[80]. These patients then experienced long-term remission after sphincterotomy.

In both of these series, botulinum toxin was effective, free of significant side effects and was relatively easy to administer, as cannulation of the papilla was not required. Unfortunately, its role as a therapy is limited by its duration of efficacy. Muscular function usually returns within two to six months after injection^[75]. If these results can be replicated and extended at other centers, botulinum toxin can act as a diagnostic trial when manometry is unavailable to predict which patients would subsequently benefit from sphincterotomy.

In conclusion, sphincter of Oddi dysfunction is a disorder that should be suspected in patients with chronic biliary pain or recurrent pancreatitis when other organic causes have been ruled out. Because of the lack of a pathologic gold standard, manometry has been adopted as the *de facto* standard diagnostic test despite the fact that it does not have perfect correlation with outcome to therapy, it is invasive and it is available only at specialized centers. In patients with Type I SOD, a good response to sphincterotomy can be predicted regardless of manometric findings, and these patients should proceed directly to sphincterotomy (Figure 1). Type II SOD patients are the group who can most benefit from manometry to select patients for sphincterotomy. If manometry is not available, hepatobiliary scintigraphy or possibly a botulinum toxin trial can be used instead to predict response to sphincterotomy. Finally, Type III SOD patients pose a particular therapeutic challenge and likely represent a chronic pain disorder or dysmotility syndrome. The risks of manometry in this group outweigh the benefits and here scintigraphic studies

or a botulinum toxin trial may also be effective in predicting response to sphincterotomy. Further research is needed in many areas regarding sphincter of Oddi dysfunction. Larger trials of non-invasive diagnostic modalities are needed, with therapeutic outcome as an endpoint. Clinical trials comparing outcomes to sphincterotomy after selection with manometry compared to empiric sphincterotomy would guide therapy in Type II patients. Finally, there is little information regarding treatment of patients who have an incomplete response to sphincterotomy. Answering these questions will bring us closer to a more evidence-based mode of managing these patients.

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