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PANCREAS AND BILIARY TRACT

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Background: In sphincter of Oddi dysfunction (SOD), sphincter of Oddi manometry (SOM) predicts the response to sphincterotomy, but is invasive and associated with complications.

Aim: To evaluate the role of secretin-stimulated magnetic resonance cholangiopancreatography (ss-MRCP) in predicting the results of SOM in patients with suspected type II or III SOD.

Methods: MRCP was performed at baseline and at 1, 3, 5 and 7 min after intravenous secretin. SOD was diagnosed when the mean basal sphincter pressure at SOM was >40 mm Hg. Long-term outcome after SOM, with or without endoscopic sphincterotomy, was assessed using an 11-point (0–10) Likert scale.

Results: Of 47 patients (male/female 9/38; mean age 46 years; range 27–69 years) referred for SOM, 27 (57%) had SOD and underwent biliary and/or pancreatic sphincterotomy. ss-MRCP was abnormal in 10/16 (63%) type II and 0/11 type III SOD cases. The diagnostic accuracy of ss-MRCP for SOD types II and III was 73% and 46%, respectively. During a mean follow-up of 31.6 (range 17–44) months, patients with normal SOM and SOD type II experienced a significant reduction in symptoms (mean Likert score 8 vs 4; $p=0.03$, and 9 vs 1.6; $p=0.0002$, respectively), whereas in patients with SOD type III, there was no improvement in pain scores. All patients with SOD and an abnormal ss-MRCP ($n=12$) reported long-term symptom improvement (mean Likert score 9.2 v 1.2, $p<0.001$).

Conclusions: ss-MRCP is insensitive in predicting abnormal manometry in patients with suspected type III SOD, but is useful in selecting patients with suspected SOD II who are most likely to benefit from endotherapy.

Sphincter of Oddi dysfunction (SOD) forms part of the clinical spectrum of functional gastrointestinal disorders and is defined as an abnormality of sphincter of Oddi contractility, which causes pancreaticobiliary-type pain, cholestasis and/or pancreatitis.¹ Sphincter of Oddi manometry (SOM) is the gold standard for the diagnosis of SOD, and has a particular role in selecting for treatment patients with type II (pancreaticobiliary-type pain and duct dilatation or abnormal liver biochemistry/recurrent pancreatitis) and type III (pain alone) SOD, who are most likely to benefit from endoscopic sphincterotomy.² However, SOM is an invasive procedure with a 4–30% morbidity (pancreatitis, cholangitis, septic complications and anaesthetic risks) and up to 0.4% mortality.^{3–4} Most reports also indicate that patients with SOD have a complication rate from endoscopic sphincterotomy about 2–4 times that of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) for bile duct stones,^{5–6} with suspected SOD an independent risk factor for post-ERCP pancreatitis on multivariate analysis.⁷ To reduce the clinical morbidity associated with SOM, a number of non-invasive tests have been proposed. These include the morphine–prostigmin provocative test (Nardi Test),⁸ ultrasound–secretin test,⁹ endoscopic ultrasound–secretin test,¹⁰ fatty-meal-stimulated ultrasonography and hepatobiliary scintigraphy.^{11–12} However, in general, the clinical utility of these tests is limited owing to their relatively low sensitivity and specificity in predicting the presence of SOD and their poor correlation with outcome after sphincter ablation.

Magnetic resonance cholangiopancreatography (MRCP) has largely replaced diagnostic ERCP in clinical practice, because it is non-invasive, does not require sedation and permits the accurate assessment of parenchymal and ductal abnormalities within the pancreaticobiliary system.¹³ The concomitant use of

intravenous secretin to relax the sphincter of Oddi and stimulate the flow of pancreatic exocrine juice and bile¹⁴ has been reported to improve the delineation of the pancreatic and common bile ducts at MRCP (secretin-stimulated (ss)-MRCP),¹⁵ but its use in patients with suspected SOD has been limited.

The aim of this prospective study was to compare the non-invasive test of ss-MRCP with the gold standard of SOM in patients with suspected biliary or pancreatic types II and III SOD.

PATIENTS AND METHODS

Patient selection

Patients were recruited for the study during a 2-year period. Inclusion criteria were (1) age >18 years; (2) recurrent pancreaticobiliary-type pain for at least 6 months, which had not responded to medical treatment and required at least intermittent opiate analgesia and/or hospital admission; and (3) unexplained biochemically proved recurrent pancreatitis for which previous non-invasive imaging by oesophagogastroduodenoscopy, transabdominal ultrasound and/or abdominal CT and laboratory tests had failed to identify a cause. Exclusion criteria included current alcohol misuse, pregnancy or lactation, inability to give consent or tolerate MRCP, and any serious comorbidity precluding sedated endoscopy. Cases where an alternative aetiology for the patient's symptoms (eg, bile duct stones, tumours) were identified during ERCP were also

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; HBS, hepatobiliary scintigraphy; ss-MRCP, secretin-stimulated magnetic resonance cholangiopancreatography; NPV, negative predictive value; PPV, positive predictive value; SOD, sphincter of Oddi dysfunction; SOM, sphincter of Oddi manometry

excluded. The study was approved by the Joint UCL/UCLH Committees on the Ethics of Human Research, and written informed consent was obtained from all patients.

Definition of end points

The primary end point of the study was to compare the non-invasive test of ss-MRCP with the gold standard of SOM in patients with suspected biliary or pancreatic types II and III SOD, as defined by the modified Hogan–Geenen criteria, which excludes drainage time.²

The secondary end points were to (1) evaluate the risk of post-ERCP pancreatitis in patients with suspected SOD who undergo SOM with or without endoscopic sphincterotomy and (2) assess the long-term outcome of patients with suspected SOD after SOM with or without endoscopic sphincterotomy.

The diagnosis of biliary type II SOD was made if patients presented with recurrent biliary-type pain and had raised liver biochemical tests documented on ≥ 2 occasions, or a common bile duct diameter >12 mm. Patients with biliary type III SOD had recurrent biliary-type pain alone. The diagnosis of pancreatic type II SOD was made in patients with recurrent pancreatic-type pain and a raised serum amylase/lipase or pancreatic duct dilatation >5 mm. Patients with pancreatic type III SOD had recurrent pancreatic-type pain alone.² Patients were assessed clinically before SOM and at the time of clinic review, or by telephone after discharge, by an investigator who was blinded to the results of SOM. Each patient was asked to evaluate his/her symptoms on an 11-point Likert Scale (0, no pain at all; 10, worst pain imaginable). Patients were first asked to rate their worst pain for a 1-week period before investigation and then to rate their worst pain for a 1-week period before the final review.

Post-ERCP pancreatitis was defined as epigastric pain radiating to the back with associated tenderness to palpation, neither having been present before ERCP, and an increase in the serum amylase level to >3 times the normal value that persisted on the day after ERCP. Severity of post-ERCP pancreatitis was graded as mild, moderate or severe, as described previously.¹⁶

Magnetic resonance cholangiopancreatography

The baseline MRCP images were obtained using standard breath-hold, heavily T2-weighted, fat-suppressed fast spin-echo images (five 10–15 mm coronal sections) on a Siemens 1.5T MR system (Siemens Medical Solutions, Oldbury, UK). MRCP was then repeated at 1, 3, 5 and 7 min after stimulation with intravenous secretin (1 IU/kg “Secrelux”, Sanochemia Pharmazeutika AG, Wien, Germany). Image analysis included measurement of pancreatic and common bile duct diameters before and after secretin stimulation, and both quantitative and qualitative assessments of the change in fluid volume in the small intestine. A >1 mm increase in duct diameter 3 min after secretin infusion and/or duct dilatation that persisted at 7 min after secretin administration were considered suggestive of SOD.¹⁷ Normal qualitative exocrine function was defined as filling of the second portion of the duodenum including the junction between the second and third duodenal portions at 7 min. All MRCP studies were reported by a radiologist who was blinded to the SOM findings.

SOM and endoscopic sphincterotomy

ERCP and SOM were performed by two experienced endoscopists (SP and AH). The patients were sedated with midazolam and either fentanyl or pethidine; hyoscine butylbromide (buscopan) was not administered. SOM was performed using a 5-Fr wire-guided triple-lumen water-perfused manometry catheter (Lehman, Wilson-Cook Medical, Winston-Salem, USA). This

catheter contains two side-hole orifices for pressure sensing, which are spaced about 2 mm apart. The manometry catheter was introduced either directly or advanced over a 0.018-inch guidewire (Roadrunner, Wilson-Cook Medical, Winston-Salem, USA) into the common bile duct and pancreatic duct. The catheter position was confirmed fluoroscopically and by aspiration of clear (pancreatic) or yellow (bile) fluid. Each catheter lumen was then perfused separately using a low-compliance pneumohydraulic capillary infusion system equipped with strain-gauge transducers (Oakfield Instruments, Eynsham, UK), which perfused the recording channels of the catheter continuously with sterile deionised bubble-free water at a pressure of 7.5 psi and a constant rate of 0.25 ml/min. To reduce the risk of pancreatitis, aspiration was performed through the middle port and pressure was recorded from the other two ports.¹⁸ Pressure tracings were digitised by a digital manometry sensor (Flexilog 3000, Oakfield Instruments) and displayed on a standard personal computer.

The catheter was withdrawn at 1 mm intervals while continuous pressure measurements were being taken (the “station pull-through technique”). Sphincter of Oddi basal pressure was defined as the difference between the duodenal pressure and that of the base of the phasic waves. Manometric values were considered abnormal if the average sphincter of Oddi basal pressure was >40 mm Hg above the duodenal pressure (sustained for >30 s and observed in both leads).^{19, 20}

In patients with manometrically proved SOD, an endoscopic sphincterotomy of the affected segment (biliary, pancreatic or both) was performed using a traction-type papillotome (Wilson-Cook) during the same procedure, usually with the placement of a pancreatic duct stent that was removed within 3–5 days.^{21, 22} All patients were admitted overnight and monitored for complications related to their endoscopic procedure. After discharge, patients were followed up in a specialist pancreaticobiliary clinic to assess their clinical progress.

Statistical analysis

Sensitivity, specificity, positive and negative predictive values (PPV and NPV) and diagnostic accuracy for the overall cohort of patients and those with SOD type II were calculated for ss-MRCP. Accuracy was determined by summation of the “true positives” and “true negatives” in the patient cohort. Grouped data are presented as means (standard deviation (SD)). The significance of differences regarding the long-term outcome between groups was tested with the Student’s *t* test (two tailed). Categorical data were examined using the χ^2 test with Yate’s correction or Fisher’s exact test as appropriate; $p \leq 0.05$ was considered significant. All statistical analyses were performed using SPSS V.10.0.

Table 1 Comparison of sphincter of Oddi manometry with secretin-stimulated magnetic resonance cholangiopancreatography in the diagnosis of sphincter of Oddi dysfunction

	SOM (n)		
	Normal	Abnormal	Total
ss-MRCP (n)			
Normal	11	17	28
Abnormal	2	10	12
Total	13	27	40

SOM, sphincter of Oddi manometry; ss-MRCP, secretin-stimulated magnetic resonance cholangiopancreatography.

The two patients with abnormal ss-MRCP and normal SOM presented with recurrent pancreaticobiliary type pain alone (suspected sphincter of Oddi dysfunction type III).

Table 2 Comparison of biliary sphincter of Oddi manometry with secretin-stimulated magnetic resonance cholangiopancreatography in the diagnosis of biliary sphincter of Oddi dysfunction

	Biliary SOM (n)		
	Normal	Abnormal	Total
ss-MRCP (n)			
Normal	22	10	32
Abnormal	2	6	8
Total	24	16	40

SOM, sphincter of Oddi manometry; ss-MRCP, secretin-stimulated magnetic resonance cholangiopancreatography.

RESULTS

Primary end point

During the study period, 47 patients (9 men and 38 women, mean age 46 years, range 22–69 years) with suspected biliary or pancreatic type SOD II or III were referred from a total of 28 hospitals to University College Hospital, London, UK, and were enrolled into the study. The mean duration of symptoms was 35 (range 6–172) months. In all, 9 (19%) patients had a history of transiently abnormal liver biochemistry, and 13 (28%) patients had had at least one episode of pancreatitis. Also, 27 (57%) patients had had cholecystectomy, and 7 (15%) had previously undergone an endoscopic biliary sphincterotomy empirically, without SOM. All patients underwent ss-MRCP and SOM of the biliary and/or pancreatic sphincters; there were no complete cannulation failures.

A total of 13 (28%) patients (all male; mean age 42 years; range 27–65 years) had a normal ERCP, SOM and ss-MRCP. Seven patients (3 male and 4 female; mean age 49 years; range 22–67 years) with normal SOM were found to have morphological changes of chronic pancreatitis on both ERCP and ss-MRCP, and were excluded.

In all, 27 (57%) patients had manometrically proved SOD with a basal pressure in one or both sphincters >40 mm Hg, a result that was considered to be a true positive diagnosis of SOD. A total of 16 patients (2 male and 14 female; mean age 48 years; range 27–69 years) were diagnosed as having type II SOD (8 biliary, 7 pancreatic and 1 both sphincters), and 11 patients (4 male and 7 female; mean age 46 years; range 34–57 years) had type III SOD (6 biliary, 4 pancreatic and 1 both sphincters). ss-MRCP was abnormal in 10 of 16 patients with type II SOD and in 0 of 11 patients with type III SOD. Compared with SOM, the overall sensitivity, specificity, PPV, NPV and diagnostic accuracy of ss-MRCP in types II and III SOD were 37%, 85%, 83%, 39% and 52.5%, respectively (table 1). The sensitivity, specificity, PPV, NPV and diagnostic accuracy of ss-MRCP in the diagnosis of SOD type II alone were 62.5%, 85%, 83%, 65% and 73%, respectively.

ss-MRCP was abnormal in 6 of 16 (37.5%) patients with manometrically proved biliary SOD as compared with 4 of 13 (30.7%) patients with pancreatic SOD ($p = 0.99$). Two patients were diagnosed with SOD of the biliary and pancreatic segment of the sphincter. Table 2 shows the correlation of ss-MRCP with biliary SOM.

Secondary end points

During a mean (SD) follow-up of 28 (9.2) months (range 17–44 months), 9 of 13 (69%) patients with normal SOM reported that their symptoms had improved without sphincterotomy, with the mean (SD) score on the Likert Scale falling from 8 (0.9) to 4 (0.3; $p = 0.03$).

A total of 14 of 16 (87%) patients with manometrically proved SOD type II reported improvement in symptoms after

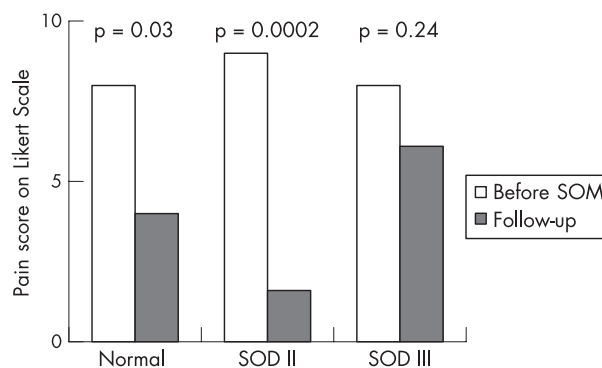


Figure 1 Long-term symptomatic outcome of patients with normal sphincter of Oddi manometry (SOM) and sphincter of Oddi dysfunction (SOD) types II and III after a mean follow-up of 31.6 months (range 17–44 months).

endotherapy, with a mean (SD) score before SOM of 9 (1) falling to 1.6 (3.1) during a mean (SD) follow-up of 35.1 (6.5) months (range 24–42 months; $p = 0.0002$). By contrast, only 2 of 11 (18%) patients with manometrically proved SOD type III reported benefit after endoscopic treatment. The mean (SD) score on the Likert Scale before SOM was 8 (1.1), compared with a score of 6.1 (2.9) after a mean (SD) follow-up of 30.2 (6.3) months (range 20–37 months; $p = 0.24$; fig 1). Patients with manometrically proved SOD II were most likely to benefit from endotherapy on long-term follow-up compared with those with SOD III and raised sphincter pressures ($p = 0.0009$).

All patients with an abnormal ss-MRCP ($n = 12$) reported symptomatic benefit during long-term follow-up as opposed to 13 of 28 (46%) patients with normal ss-MRCP ($p = 0.001$). The mean (SD) score on the Likert Scale in patients with an abnormal ss-MRCP fell from 9.2 (0.7) to 1.2 (0.4) during a mean (SD) follow-up of 31 (6.8) months ($p < 0.001$). In patients with normal ss-MRCP, the mean (SD) score on the Likert Scale fell from 8 (1.4) to 6 (3.2) during a mean (SD) follow-up of 31.7 (10.2) months ($p = 0.05$).

In all, 5 (10.6%) patients developed post-ERCP pancreatitis (4 mild and 1 moderate), requiring a mean hospital stay of 4.6 (range 3–7) days. One of those patients had SOD type II and four had SOD type III (table 3). There was a trend towards an increased risk of post-ERCP pancreatitis in patients with SOD type III compared with patients with SOD type II ($p = 0.125$). None of the patients who underwent SOM alone (without endoscopic sphincterotomy) developed any complications. The risk of post-ERCP pancreatitis was significantly higher in the patients with SOD type III compared with those with normal SOM ($p = 0.031$). One patient with SOD type III had a small retroperitoneal perforation after biliary sphincterotomy that settled with conservative management during a 16-day hospitalisation, giving a total complication rate of 12.8% in the 47 patients.

DISCUSSION

SOM is regarded as the gold standard for the diagnosis of SOD and predicts response to sphincterotomy,²³ but it is invasive and associated with complications.^{3–7} Given the technical difficulties and limited availability of SOM, interest has focused on non-invasive surrogates for SOM that might identify patients with types II and III SOD likely to benefit from sphincterotomy. In a study using hepatobiliary scintigraphy (HBS) with morphine provocation and a cut-off value of 15% radionuclide excretion at 60 min, the sensitivity and specificity for detecting raised sphincter of Oddi basal pressures in patients with SOD types II

Table 3 Risk of post-endoscopic retrograde cholangiopancreatography pancreatitis in patients with manometrically proved sphincter of Oddi dysfunction types II and III

	Post-ERCP pancreatitis		
	Type II, n = 16	Type III, n = 11	Total, n = 27 (%)
Biliary sphincterotomy (n = 14)	1/8	2/6	3/14 (21)
Pancreatic sphincterotomy (n = 11)	0/7	1/4	1/11 (9)
Dual sphincterotomy (n = 2)	0/1	1/1	1/2 (50)
Total, n (%)	1/16 (6)	4/11 (36)	5/27 (18.5)

ERCP, endoscopic retrograde cholangiopancreatography.

and III were 83% and 81%, respectively.²⁴ In a large retrospective study, Rosenblatt *et al*²⁵ reported that the combination of fatty meal sonography and HBS was useful in predicting the response to sphincterotomy in patients with manometrically documented SOD. However, some studies have reported a poor correlation between HBS and SOM.²⁶

The use of ss-MRCP in patients with suspected SOD has been limited. Preliminary data from the Indiana group showed a poor correlation between ss-MRCP and pancreatic SOM.^{27, 28} By contrast, in a study from Italy²⁹ that included 15 patients with recurrent pancreatitis, ss-MRCP and SOM were concordant in 13 patients; positive and negative diagnoses for SOD agreed in 82% and 100% of cases, respectively. This study has shown that ss-MRCP is insensitive in predicting abnormal SOM in patients with type III SOD, but is moderately accurate in the diagnosis of patients with manometrically proved type II SOD. However, ss-MRCP did correlate well with ERCP in detecting structural changes other than SOD, and emphasises the importance of initial non-invasive imaging in patients with suspected SOD to exclude other pathologies such as chronic pancreatitis. Additionally, our findings suggest that ss-MRCP may be useful in selecting patients with suspected SOD II who might benefit from endotherapy.

In this study, we used a duration of ss-MRCP shorter than described previously,^{15, 27–29} because we wanted to explore whether this approach would increase the sensitivity of the examination and improve patients' tolerance of the procedure. To date, ss-MRCP has been used mainly for the evaluation of the pancreatic segment of sphincter of Oddi. However, secretin also stimulates biliary ductal secretion and increases bile flow.¹⁴ Stimulation of secretin receptors on biliary ductal epithelium induces cyclic AMP levels, activation of intracellular cyclic AMP-dependent protein kinase and opening of cyclic AMP-dependent channels, which in turn induces a $[Cl^-]$ gradient favouring the activation of the apically located $[Cl^-]/[HCO_3^-]$ exchange and resulting in a bicarbonate-rich choleresis.

Patients with manometrically proved sphincter of Oddi abnormalities may benefit symptomatically from either biliary or pancreatic sphincterotomy, or even dual sphincterotomy. Clinical response varies among the three groups, being highest in biliary types I and II SOD, and lowest in type III SOD.^{1, 25, 30} A recent Cochrane review³¹ concluded that sphincterotomy for biliary SOD was effective for those patients with raised sphincter of Oddi pressures, but no better than placebo for those with normal sphincter of Oddi pressures. Furthermore, pancreatic sphincter hypertension has been described in 15–72% of patients with "idiopathic" recurrent pancreatitis^{22, 27, 32} and in some patients whose symptoms fail to improve after biliary endoscopic sphincterotomy.^{33, 34} In patients with persistent symptoms and increased basal pancreatic sphincter pressures, performing a pancreatic sphincterotomy has been

associated with an improvement in clinical symptoms in 15–77% of patients.³⁵ In this series, an endoscopic sphincterotomy of the affected segment was performed in all patients with manometrically proved raised sphincter of Oddi pressures. During a mean follow-up of almost 3 years, there was a marked improvement in pain scores in patients with SOD type II but not in those with SOD type III. This explains, partly, why patients with an abnormal ss-MRCP, who were diagnosed with SOD type II in 83% of cases, had a considerably higher symptomatic response during follow-up than those with normal ss-MRCP.

There are large differences in reported success rates for managing type III SOD between specialist centres. According to a recent systematic review by our group,³⁶ about 37% of such patients report long-term benefit after sphincter ablation. In this series, patients with SOD type III had a generally poor symptomatic response after endoscopic sphincterotomy of the affected segment. Additionally, these patients have the highest risk of complications of ERCP, principally pancreatitis.³⁷ Based on these results, there is a need for further prospective, controlled trials to justify the invasive management by ERCP and sphincterotomy of patients with SOD type III. The injection of botulinum toxin into the intraduodenal sphincter segment has been reported to predict the long-term outcome after endoscopic sphincterotomy in patients with manometrically proved biliary type III³⁸ and pancreatic SOD,³⁹ but further studies are needed.

In conclusion, ss-MRCP is insensitive in predicting abnormal manometry in patients with suspected type III SOD, but is moderately accurate in the diagnosis of patients with SOD type II, who are most likely to benefit from endoscopic sphincterotomy.

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