Manometry based randomised trial of endoscopic sphincterotomy for sphincter of Oddi dysfunction

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Abstract

***Background*—Endoscopic sphincterotomy for biliary-type pain after cholecystectomy remains controversial despite evidence of efficacy in some patients with a high sphincter of Oddi (SO) basal pressure (SO stenosis).**

***Aim*—To evaluate the effects of sphincterotomy in patients randomised on the basis of results from endoscopic biliary manometry.**

***Methods*—Endoscopic biliary manometry was performed in 81 patients with biliary-type pain after cholecystectomy who had a dilated bile duct on retrograde cholangiography, transient increases in liver enzymes after episodes of pain, or positive responses to challenge with morphine/neostigmine. The manometric record was categorised as SO stenosis, SO dyskinesia, or normal, after which the patient was randomised in each category to sphincterotomy or to a sham procedure in a prospective double blind study. Symptoms were assessed at intervals of three months for 24 months by an independent observer, and the effects of sphincterotomy on sphincter function were monitored by repeat manometry after three and 24 months.**

***Results*—In the SO stenosis group, symptoms improved in 11 of 13 patients treated by sphincterotomy and in five of 13 subjected to a sham procedure ($p = 0.041$). When manometric records were categorised as dyskinesia or normal, results from sphincterotomy and sham procedures did not differ. Complications were rare, but included mild pancreatitis in seven patients (14 episodes) and a collection in the right upper quadrant, presumably related to a minor perforation. At three months, the endoscopic incision was extended in 19 patients because of manometric evidence of incomplete division of the sphincter.**

***Conclusion*—In patients with presumed SO dysfunction, endoscopic sphincterotomy is helpful in those with manometric features of SO stenosis.**

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Keywords: sphincter of Oddi; manometry; endoscopic sphincterotomy; motility; bile duct; pancreas

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Sphincter of Oddi (SO) dysfunction may be responsible for symptoms in some patients with episodic biliary-type pain which persists or recurs after cholecystectomy.[1] This hypothesis is supported by the observation that some patients have dilatation of the bile duct on retrograde cholangiography, transient increases in liver enzymes with pain, or both abnormalities. In uncontrolled surgical studies, operative sphincteroplasty appeared to be helpful for pain,[2 3] and sphincter histology often disclosed abnormalities, including inflammation, muscle hypertrophy, and fibrosis.[4]

The advent of endoscopic sphincterotomy and developments in endoscopic manometry raised the possibilities of greater precision in diagnosis and management, without prolonged stays in hospital. Although early surveys suggested benefit from sphincterotomy, a prospective randomised trial by Geenen and colleagues[5] was the first to provide supporting data. In this study patient stratification according to manometric findings was performed retrospectively and showed that clinical improvement occurred only in patients with a high SO basal pressure. Similar results were reported by Neoptolemos *et al*,[6] and subsequently other prospective non-randomised trials have confirmed the benefit from sphincterotomy in patients with an elevated basal pressure.[7–9] However, in an earlier study by our group in which we retrospectively assessed the value of manometry in predicting response to sphincterotomy, no clear benefit was seen in patients with an elevated basal pressure.[10] This result highlighted the weakness of retrospective stratification of patient groups. Consequently we embarked on a prospective randomised trial based on the results from endoscopic biliary manometry. In addition, we incorporated repeat manometry after three and 24 months to ensure the presence of an adequate endoscopic incision.

Although the incidence of complications from sphincterotomy was low (about 10%) in initial reports,[11] subsequent studies reported early complications in up to 20% of patients, largely related to pancreatitis.[8 12] This highlights the importance of being able to predict which patients will respond to sphincterotomy.

Methods

The study commenced in May 1987 and was completed in October 1996 when the last recruited patient had completed 24 months follow up. The trial was centred at

Abbreviation used in this paper: SO, sphincter of Oddi.

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Patients enrolled in the study had been referred to senior clinicians for evaluation and management of recurrent abdominal pain after cholecystectomy, consistent with a biliary disorder. After appropriate clinical evaluation, which often involved upper and lower gastrointestinal endoscopy as well as computed tomography scanning of the abdomen, all of the patients underwent endoscopic retrograde cholangiopancreatography to exclude a structural cause for their pain in either the biliary or pancreatic ductal system. Those with no abnormalities (apart from ductal dilatation) were considered eligible for enrolment into the study. Patients with symptoms and signs of recurrent pancreatitis (abdominal pain with elevated serum amylase levels) were excluded from the study. Before entry into the study, all patients underwent a morphine/neostigmine provocation test,[13] at which time they were instructed on the use of a linear analogue pain chart. Entry criteria included recurrent biliary-type pain for at least six months in a patient who had undergone previous cholecystectomy plus one or more of the following: transient increases in serum aminotransferases with spontaneous episodes of pain; dilatation of the bile duct (> 12 mm) at retrograde cholangiography; positive responses to challenge with morphine/neostigmine.

After meeting the entry criteria, all patients were interviewed using a structured questionnaire to record the nature of their symptoms. Patients then completed a diary for three months which recorded the frequency and severity of pain using a linear analogue chart. This was followed by a short inpatient stay for SO manometry and treatment according to the randomisation protocol. SO manometry was performed using standard methods described below. Manometric results were categorised as normal, SO stenosis, or SO dyskinesia as described previously.[14] Within each of these three categories, patients were randomised by the draw of a card to undergo either endoscopic sphincterotomy or a sham sphincterotomy procedure. Both groups of patients were then treated as if endoscopic sphincterotomy had been performed, namely continued fasting, administration of intravenous fluids, and assessment by a clinician before commencement of oral fluids. Patients were discharged from hospital if they were clinically stable on the evening of the procedure.

Patients underwent a second manometric procedure three months after the initial investigation. In those with a previous sphincterotomy, the endoscopic incision was extended if manometric evidence of a residual sphincter was present. In those who had been randomised to the sham procedure, repeat manometry only was undertaken.

Patients were followed up at intervals of three months for two years by a clinician who was not involved with the endoscopic therapy and was unaware of the results of manometry or randomisation. Additional follow up was undertaken by a research assistant who recorded the patients' symptoms and assessed the pain diaries. At each follow up visit, the symptoms were categorised as either no change/worse, improved (if there had been considerable improvement in the incidence and severity of pain such that only occasional oral analgesics were required for mild pain), or asymptomatic (no further episodes of typical abdominal pain).

PROCEDURES

Morphine/neostigmine provocation test[13]

Patients were admitted to a day ward and a cannula was inserted into a peripheral vein. They were instructed on the use of a linear analogue pain scale, where 0 was no pain and 10 was the most severe pain they had ever experienced. Venous blood was collected at hourly intervals to determine serum levels of liver aminotransferases, alkaline phosphatase, bilirubin, and amylase. Patients were given intramuscular injections at the commencement of the study and after one hour. The first injection was of normal saline while the second included morphine 0.12 mg/kg and neostigmine 0.012 mg/kg. Venous blood was collected for up to four hours as described previously. A positive result was defined as reproduction of the pain associated with elevation, above the reference range, of either plasma aminotransferases or plasma amylase or both.

SO manometry[14]

Under mild sedation, a duodenoscope was introduced and positioned opposite the major papilla. A triple lumen manometry catheter (Arndorfer Medical Specialties, Greendale, Wisconsin, USA) was inserted into the bile duct to record duct pressures. The catheter was then withdrawn so that all three sideholes recorded SO activity. Recordings were made for at least five minutes, after which cholecystokinin octapeptide (Kinevac; Bracco Diagnostics, Mississauga, Ontario, Canada) 20 ng/kg was given as a bolus intravenous injection. The manometric tracing was evaluated immediately and the record classified as normal, SO stenosis, or SO dyskinesia.[14] Stenosis was diagnosed if the basal pressure averaged >40 mm Hg on all three recording channels. Criteria for the diagnosis of dyskinesia included an increased incidence of phasic contractions (>7/min), and/or an increased incidence of retrograde contractions (>50%), and/or a paradoxical response to cholecystokinin octapeptide (stimulation instead of inhibition).

Endoscopic sphincterotomy

This was performed using standard techniques. A Demling-type papillotome was introduced into the bile duct after which an incision had been made using coagulation and cutting current. The incision aimed to divide the entire length of the biliary sphincter. In patients undergoing a sham procedure, a papillotome

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Table 1 Numbers of patients with various criteria leading to inclusion in the study

	One criterion	*Two criteria*	*Three criteria*
Dilated CBD	11	9	9
LFT elevation	16	24	9
Positive morphine provocation	18	21	9
Total	45	27	9

CBD, common bile duct; LFT, liver function test.

was introduced into the duodenum after which the "noises" of sphincterotomy were created without proceeding to sphincterotomy. The study protocol was reviewed and approved by the ethics committee of both institutions.

DATA ANALYSIS

The major endpoint of the study was whether abdominal pain improved or remained unchanged. Consequently, the pain status of all patients was compared two years after randomisation. Comparisons were made between patients who had sphincterotomy and those randomised to a sham procedure within each manometric category as well as comparisons for other entry criteria. χ^2 analysis using Fisher's exact test was used, taking $p<0.05$ as the level of significance. The number of patients required in each group was calculated for a power of 0.8 and an alpha value of 0.05.

Results

Eighty one patients, 73 women and eight men (median age 45, range 22–71) with recurrent biliary-type pain were entered in the study. Two patients were excluded from analysis: one was lost to follow up after six months and one was withdrawn because of two episodes of pancreatitis after two manometric procedures. All patients experienced recurrent biliary-type pain which commenced a median of two years (range six months to 30 years) after cholecystectomy. Sixty four patients had undergone cholecystectomy for biliary-type pain plus gallstones, while 17 patients had undergone cholecystectomy for acalculous gallbladder disease.

Table 1 shows the number of patients with various entry criteria. Only a minority of patients had abnormalities in all three entry criteria. Satisfactory manometric records were obtained from all patients before randomisation and an endoscopic incision was possible in all patients randomised to sphincterotomy. The endoscopic incision was lengthened at three months in 19 of 37 sphincterotomy patients because of manometric evidence of residual sphincter activity, largely residual phasic activity rather than persistence of the original manometric abnormality. Of the patients randomised to sphincterotomy for SO stenosis, one had persistent stenosis at three months and a different patient had stenosis at 24 months.

Categorisation of the pain as unchanged, improved, or resolved was similar with both the patient score sheet and assessment by the independent doctor. Furthermore, categories that were agreed at six months after randomisation were generally maintained at 24 months. Table 2 shows the overall results within each manometrically defined group. In those with SO stenosis, improvement after two years was significantly more common in patients treated by sphincterotomy than in those having a sham procedure. For other manometric diagnoses, however, results after sphincterotomy and sham procedures were similar. Symptomatic outcome was independent of bile duct dilatation, changes in liver enzymes, or results from the morphine/neostigmine provocation test. Furthermore, symptom outcome was unrelated to the number (one to three) of positive entry criteria.

Table 2 Assessment of pain at 24 months in patients treated with either endoscopic sphincterotomy (ES) or a sham procedure

	Number	*Improved*	*No change*	*p Value*
SO stenosis				
Sham	13	5	8	0.041
ES	13	11	2	
SO dyskinesia				
Sham	10	5	5	0.670
ES	11	4	7	
Normal manometry				
Sham	19	8	11	0.473
ES	13	8	5	

Patients with resolution of their pain are included in the improved group. SO, sphincter of Oddi.

Complications from the procedures included mild pancreatitis in seven patients (14 episodes) and a minor perforation of the duodenum in one patient. Pancreatitis prolonged hospital stay by a median of eight days and was more common in patients with the manometric diagnosis of SO stenosis. There were no deaths as a result of the procedures.

Discussion

When compared with previous studies, the distinctive feature of this study included randomisation on the basis of results of SO manometry and repeat manometry to confirm adequacy of the endoscopic incision. In relation to entry criteria, the study differed from previous reports only by the inclusion of patients with positive responses to challenge with morphine/neostigmine.

In this study, 26 of 81 patients (32%) had manometric evidence of SO stenosis. After randomisation to sphincterotomy or a sham procedure, 11 of the 13 (85%) improved after sphincterotomy and five of the 13 (38%) improved after a sham procedure ($p = 0.041$). These results are similar to previous studies from the United States[5] and the United Kingdom,[6] in which the manometry was evaluated retrospectively, both in response rates to sphincterotomy and in responses to a sham procedure.

Large differences between the sphincterotomy and the sham groups were expected in this study, and accordingly the study design meant that improvements of more than 40% were detectable as statistically significant, as seen in the SO stenosis group. However, we were unable to demonstrate improvement in the other groups, but this may represent a statistical type II error.

It remains perplexing as to why patients with SO dyskinesia do not respond to SO division.

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One possible explanation may be that patients with SO stenosis have more advanced disease than those with SO dyskinesia. Alternatively, those with SO stenosis may have a predominant disorder of the sphincter whereas those with SO dyskinesia may have changes in sphincter motility as a manifestation of a more generalised motility disorder of the gastrointestinal tract. The latter would be much less likely to respond to sphincterotomy.

An assessment was also made as to whether bile duct dilatation, changes in liver enzymes, or response to morphine/neostigmine provocation would facilitate the selection of patients for sphincterotomy. In this study, there was no relation between outcome after sphincterotomy and the presence or absence of the above features, either alone or in combination. However, previous studies from our departments have shown an association between abnormal results from morphine/neostigmine provocation and abnormal results from endoscopic manometry.[15]

Other diagnostic procedures have been suggested for SO dysfunction. Biliary scintigraphy has been shown in two small studies to have high specificity and sensitivity for SO stenosis.[16 17] Scintigraphy has also been shown to return to normal after sphincterotomy. However, the scintigraphic variables being assessed are not uniform, and further studies in this area are required before scintigraphy replaces manometry. No study has as yet assessed the response to sphincterotomy based solely on the results of scintigraphy. Symptomatic improvement with common bile duct stenting has been shown in one study to predict response to sphincterotomy.[18] However, in another study there was a high rate of pancreatitis,[19] and more studies are required before this approach can be recommended.

A potential problem in studies of this type is variation in the severity of symptoms over time. This did not appear to complicate this study as patients who improved after six months continued to show improvement at 24 months. Similarly, patients who were unchanged after three to six months almost always continued in this category for the duration of the study.

Complications from the various procedures resulted in recurrent pancreatitis in seven patients (9%) and a retroperitoneal abscess in one patient, presumably related to a minor perforation of the duodenum. Pancreatitis is a well recognised complication of endoscopic manometry and is more common in patients with manometric evidence of SO stenosis.[20] Endoscopic sphincterotomy may also result in pancreatitis but, in our experience, manometry, which is followed by sphincterotomy, does not appear to result in additional risks.[20] Nevertheless, both manometry and sphincterotomy may be technically difficult in some of these patients, and higher complication rates (as well as death) have been reported.[11]

SO stenosis is characterised by an elevated sphincter basal pressure. This manometric finding is reproducible in patients who have been studied on more than one occasion,[21] but the pathological correlates of SO stenosis remain unclear. One possibility is inflammation in sphincteric glands (papillitis) with the subsequent development of fibrosis. Another possibility is hypertrophy and loss of compliance within the sphincter, perhaps as a result of prolonged autonomic dysfunction. The latter explanation would be more consistent with anomalous responses to morphine as these depend on the presence of sphincteric smooth muscle.[13 15] In addition, at least some patients with SO dysfunction have endoscopic and radiological features of an elongated and thickened sphincter at the time of endoscopic retrograde cholangiopancreatography. Although the length of the endoscopic incision appeared to be adequate at the time of the initial procedure, it was lengthened in half of the patients at three months because of manometric evidence of residual sphincter activity. This is the first study in which SO motility was reassessed three months after sphincterotomy for SO stenosis. It suggests that, in patients who do not respond to sphincterotomy, repeat manometry is warranted to see whether a remaining active sphincter is present.

Results from this study support the continued use of endoscopic manometry in the evaluation of patients with episodic pain after cholecystectomy. In this as in other studies,[5 6] endoscopic sphincterotomy relieved the symptoms of pain in patients with manometric features of SO stenosis. Improvement in symptoms persisted for two years in this study and up to four years in the study by Geenen *et al*.[5] An unresolved issue is the pathogenesis of motility disorders involving the SO, and their relation to more generalised functional disorders of the gastrointestinal tract, often broadly categorised as irritable bowel syndrome.

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