

Endoscopic sphincterotomy in patients with stenosis of ampulla of Vater: Three-year follow-up of exocrine pancreatic function and clinical symptoms

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Abstract

AIM: To investigate retrospectively the long-term effect of endoscopic sphincterotomy (ES) including exocrine pancreatic function in patients with stenosis of ampulla of Vater.

METHODS: After diagnostic endoscopic retrograde cholangiopancreatography (ERCP) and ES because of stenosis of the ampulla of Vater (SOD Type I), follow-up examinations were performed in 60 patients (mean follow-up time 37.7 mo). Patients were asked about clinical signs and symptoms at present and before intervention using a standard questionnaire. Before and after ES exocrine pancreatic function was assessed by determination of immunoreactive fecal elastase 1. Serum enzymes indicating cholestasis as well as serum lipase and amylase were measured.

RESULTS: Eighty percent of patients reported an improvement in their general condition after ES. The fecal elastase 1 concentrations (FEC) in all patients increased significantly after ES. This effect was even more marked in patients with pathologically low concentrations (< 200 µg/g) of fecal elastase prior to ES. The levels of serum lipase and amylase as well as serum alkaline phosphatase (AP) and gamma-glutamyltranspeptidase (GGT) decreased significantly after ES.

CONCLUSION: The results of this study demonstrate that patients with stenosis of the ampulla of Vater can be successfully treated with endoscopic sphincterotomy. The positive effect is not only indicated by sustained improvement of clinical symptoms and cholestasis but also by improvement of exocrine pancreatic function.

INTRODUCTION

Endoscopic sphincterotomy (ES) has been introduced as a treatment for sphincter of Oddi dysfunction (SOD)^[1,2]. At least in SOD type I, which is caused by structural changes of the papilla in the majority of patients, ES is the treatment of choice^[3,4]. In most of the recent papers the focus of clinical interest has been put on aspects of cholestasis.

Gallstones, bile duct microlithiasis and sludge may repeatedly induce ductal lesions leading to obstruction and stenosis of the papilla of Vater^[5-7]. In addition to the resulting problems concerning the bile duct system, chronic obstruction of the papilla of Vater may also contribute to lesions of the pancreas. This might also play a role in the pathogenesis of chronic pancreatitis. Segmental or diffuse dilation of the main pancreatic duct as part of the spectrum of chronic pancreatitis has given rise to the concept of obstruction and pancreatic ductal hypertension as an important pathogenetic mechanism of chronic pancreatitis^[8,9]. Data from an autopsy study also showed that the incidence of chronic pancreatitis is higher in patients with gallstones which emphasises the role of gallstones, sludge and papillary stenosis in the pathogenesis of chronic pancreatitis^[10].

The former gold standard imaging technique, endoscopic retrograde cholangiopancreatography (ERCP), is based on ductal abnormalities. Pancreatographic changes correlate with exocrine dysfunction^[11]. As an indirect pancreatic function test measurement of fecal elastase-1 concentrations (FEC) shows a 93%-100% sensitivity for moderate and 96%-100% sensitivity for severe exocrine pancreatic insufficiency as well as a specificity of 93%-98%^[12,13].

The aim of this study was to investigate the long-term effects of ES not only regarding clinical symptoms

and parameters of cholestasis, but also with a focus on exocrine pancreatic function.

MATERIALS AND METHODS

Patients

Nineteen male and 41 female patients aged between 21 and 80 years (mean age 57.4 ± 15.2 years) were investigated retrospectively. The follow-up period averaged 37.7 ± 7.0 mo (ranging from 28-51 mo). The mean body mass index was 24.4 ± 4.0 kg/m² (ranging from 18.4-35.5 kg/m²).

All patients, who initially presented with signs of either cholestasis or pancreatic inflammation and abdominal complaints, underwent ERCP and endoscopic sphincterotomy (ES) in our department after giving their informed consent. The period between the first ES and follow-up averaged 37.7 mo. Follow-up consisted of assessing clinical and laboratory data of the patients before and after ES by using the patients' records and personal interviewing based on a standardized questionnaire. Patients with malignancy of the pancreas and/or the bile duct system were not included.

ERCP and ES

All patients underwent ERCP and ES in our department. All procedures were performed by one experienced investigator using standard techniques. Radiological changes of the pancreatic duct system were evaluated according to the Cambridge classification^[14]. In all patients ES was performed because of SOD type 1 [clinical symptoms, laboratory findings and findings in imaging techniques (ultrasound or ERCP)]. For ES a single use precurved sphincterotome (Wilson-Cook Medical Inc., NC, USA) and a single use guidewire 0.18 inch (Medwork, Neuss, Germany) were used. ES was performed as sphincterotomy of the pancreatic and/or biliary segment of the sphincter of Oddi. Some patients underwent ES more than once because of recurrent symptoms and/or signs of cholestasis and/or pancreatic inflammation. In some cases a precut of the papilla was necessary.

Questionnaire

The questionnaire included the following items: age, sex, and body mass index (BMI). The intensity of clinical symptoms such as nausea, emesis, and quantity of abdominal pain were assessed using the visual analogue scale (0 = not present, 10 = maximum complaint).

Laboratory methods

Blood samples were taken routinely prior to and after ES and checked for the following parameters: serum lipase (normal range 20-160 U/L), serum alpha-amylase (< 53 U/L), serum aspartate aminotransferase (AST/SGOT; male 5-20, female 5-17 U/L), serum alanine aminotransferase (ALT/SGPT; male 5-23, female 5-17 U/L), alkaline phosphatase (AP; male adult 60-170 U/L, female adult 40-160 U/L), gamma-glutamyltranspeptidase (GGT; male 6-28 U/L, female 4-18 U/L), and bilirubin (< 1.0 mg/dL). Fecal elastase-1 was determined by ELISA using two monoclonal antibodies specific for human

Table 1 ERCP findings in 60 patients

	Patients n (%)
Papilla	
Papillitis (chronic/acute)	20 (33)
Periampullary diverticulum	7 (12)
Pancreas	
Pancreas divisum	0
Pancreatitis Cambridge 0	2 (3)
Pancreatitis Cambridge I	11 (18)
Pancreatitis Cambridge II	25 (42)
Pancreatitis Cambridge III	10 (17)
No pancreatogram	12 (20)
Bile duct system	
Cholangitis	10 (17)
Biliary sludge and stones	15 (25)
Bile duct dilation (any)	31 (52)
Common bile duct stenosis	4 (6)
Negative cholecystography	7 (12)

Table 2 Amount and kind of sphincterotomies in 60 patients

	Patients n (%)
Biliary sphincterotomy	35 (58)
Pancreatic spincterotomy	3 (5)
Both	22 (37)
Amount of necessary sphincterotomies	
One	34 (57)
Two	10 (17)
Three	9 (15)
Four and more	7 (12)

elastase-1, which bind to different epitopes of the enzyme (elastase-1 stool kit; Schebo-Biotech, Giessen, Germany). Results were expressed in $\mu\text{g/g}$ stool. Values < 200 $\mu\text{g/g}$ were considered to represent exocrine insufficiency, values > 200 $\mu\text{g/g}$ were regarded as normal.

Statistical analysis

Results are expressed as mean \pm SD and range of values if not otherwise indicated. Statistics were carried out by the Statistical Package for Social Sciences (SPSS) for Windows, version 11.01. Wilcoxon-test was performed to test for significant differences between pre-treatment and post-treatment values. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows findings in ERCP, Table 2 indicates the amount as well as the kind of ES (biliary/pancreatic sphincterotomy). Fifty patients (83%) showed either impaired exocrine pancreatic function (fecal elastase-1 < 200 $\mu\text{g/g}$) or were classified as Cambridge I-III based on radiological changes of the pancreas irrespective of the initial indication for ERCP.

Clinical symptoms

After ES, 80% of the patients reported a general relief of

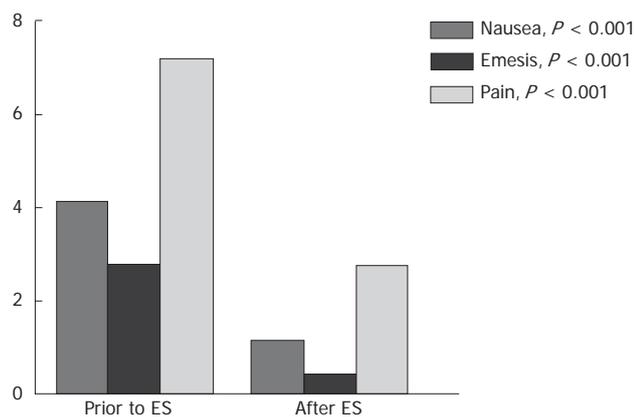


Figure 1 Clinical symptoms prior to and after endoscopic sphincterotomy due to the visual analogue scale (0 = not present, 10 = maximum complaint), $n = 55$.

symptoms, 6.7% reported the same general condition by their own assessment, whereas only 5.0% reported a worse condition. No data were given in 8.3% of all patients. There was a significant reduction of clinical symptoms such as nausea, emesis and abdominal pain after ES (Figure 1).

Laboratory findings

Serum enzymes indicating cholestasis such as Gamma-glutamyltranspeptidase, alkaline phosphatase and bilirubin showed a significant reduction after ES. Serum alpha-amylase and serum lipase also significantly decreased to normal levels after ES (data given in Table 3).

Exocrine pancreatic function

In all the 60 patients, fecal elastase-1 increased significantly from a mean of $264.38 \pm 184.01 \mu\text{g/g}$ (range 10-741 $\mu\text{g/g}$) prior to ES to $337.05 \pm 185.35 \mu\text{g/g}$ (range 10-816 $\mu\text{g/g}$) after ES ($P < 0.05$) (Figure 2). In patients with very low levels of fecal elastase-1 ($< 200 \mu\text{g/g}$) prior to ES, fecal elastase-1 rose significantly from a mean of $82.46 \pm 60.22 \mu\text{g/g}$ (range 15-187 $\mu\text{g/g}$) to $253.42 \pm 200.18 \mu\text{g/g}$ (range 10-705 $\mu\text{g/g}$) after ES ($P = 0.001$). In seven patients with fecal elastase-1 levels between 200 and 300 $\mu\text{g/g}$ prior to ES, fecal elastase-1 increased significantly from a mean of $262 \pm 36.47 \mu\text{g/g}$ (range 212-297 $\mu\text{g/g}$) prior to ES to $442.29 \mu\text{g/g}$ (range 360-610 $\mu\text{g/g}$) after ES ($P = 0.018$).

DISCUSSION

In sphincter of Oddi dysfunction (SOD), especially in type 1 displaying structural changes of the papilla in most cases, endoscopic sphincterotomy (ES) has been introduced as a definitive treatment^[3]. Most of the available research efforts focus on the beneficial effects of ES concerning clinical symptoms and parameters of cholestasis. In the present study all patients with cholestatic problems prior to ES showed an improvement after treatment. In 94% of our patients biliary sphincterotomy could effectively improve cholestasis as indicated by the normalized GGT and AP. Obviously these positive effects, lasting a mean of three years so far, are results from optimized biliary drainage without stenting. This is remarkable because pancreatobiliary drainage by endoscopic placement of an

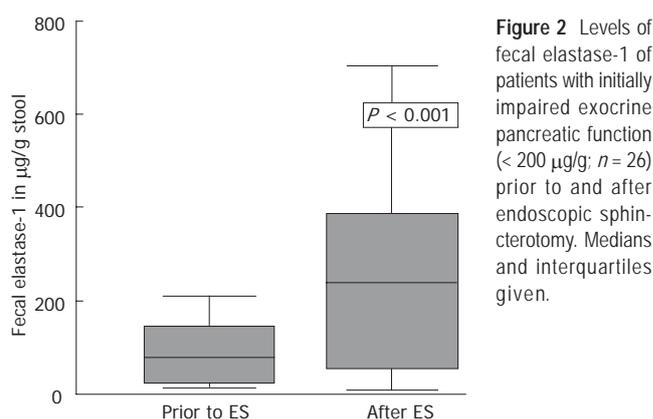


Figure 2 Levels of fecal elastase-1 of patients with initially impaired exocrine pancreatic function ($< 200 \mu\text{g/g}$; $n = 26$) prior to and after endoscopic sphincterotomy. Medians and interquartiles given.

Table 3 Levels of GGT, AP, bilirubin, serum lipase and serum alpha-amylase in all patients ($n = 60$) prior to and after endoscopic sphincterotomy (mean \pm SD)

	Prior to ES	After ES	P
GGT (U/L)	102.13 ± 146.21 (range 4-711)	41.02 ± 69.24 (range 7-337)	$= 0.001$
AP (U/L)	205.23 ± 214.88 (35-1645)	146.62 ± 135.2 (36-1047)	$= 0.001$
Bilirubin (mg/dL)	1.4 ± 2.44 (0.3-15.0)	0.65 ± 0.75 (0.1-6.0)	< 0.001
Serum lipase (U/L)	817.37 ± 1391.45 (11-7200)	29.60 ± 13.18 (6-71)	< 0.001
Serum amylase (U/L)	192.92 ± 336.44 (15-1714)	61.63 ± 19.98 (21-102)	< 0.05

ES: Endoscopic sphincterotomy.

endoprosthesis (needing exchange of stents at intervals of 2 to 4 mo) is accompanied with complications and shows poor long-term results^[15,16].

Since papillary stenosis has been suggested to play a possible role as a pathogenetic factor in pancreatitis^[6,17,18], the present study included patients with pancreatitis type symptoms and focused on changes in exocrine pancreatic function. Therapeutical approaches in patients with chronic pancreatitis aim to alleviate pain, prevent attacks of pancreatitis, reduce the effects of pancreatic insufficiency and manage complications no matter what the etiology of chronic pancreatitis might be. Medical management may include oral analgesics, enzymatic replacement, diet, and abstinence from alcohol. If obstruction of the pancreatic duct is present, invasive options must be considered. Endoscopic therapeutic techniques such as insertion of endoprosthesis, balloon or catheter dilation or sphincterotomy are applied increasingly^[19]. The facilitation of pancreatic ductal drainage should lead to a reduction of ductal pressure which is the rationale for the endoscopic intervention. The exact role of increased pressure in the pancreatic ductal system in the pathogenesis of chronic pancreatitis is not known, although elevated pressures have been documented in different animal models and human beings^[20-22]. It was reported that patients with chronic pancreatitis and pain have higher main pancreatic duct pressures than controls and experience pain relief after surgical decompression^[23]. Cholelithiasis, bile duct microlithiasis and biliary sludge might induce

papillitis or papillary stenosis followed by recurrent or permanent elevation of pancreatic ductal pressure with the consequence of chronic pancreatitis. This role of cholelithiasis and sludge in the pathogenesis of chronic pancreatitis still remains a controversy. However, several reports indicate that in patients who are thought to have 'idiopathic' pancreatitis, bile duct microlithiasis, sludge and bile crystals may account for the pancreatitis^[24-28]. There are individual reports on patients with sphincter of Oddi dysfunction or stenosis and recurrent episodes of pancreatitis which have been treated successfully with sphincterotomy.

In this study the long term effect of ES on pancreatic function and clinical symptoms of 60 patients with stenosis of ampulla of Vater was investigated. Regarding the clinical symptoms such as abdominal pain, nausea and emesis, most of our patients (80%) experienced a long-term improvement after ES. In the majority of patients we could also observe an improvement of exocrine pancreatic function as measured by FEC. It must be stressed that the follow-up study was performed at least 28 mo (maximum 51 mo) after endoscopic treatment. Other studies have reported similar immediate symptomatic improvements in patients who underwent dilation of the pancreatic duct followed by placement of an endoprosthesis, but the long-term results are not very promising as symptomatic stent occlusion often occurs^[15,29]. As reported elsewhere^[30], in some of our patients several sphincterotomies (up to six) had to be performed, if symptoms and pathological laboratory findings persisted. It appears possible, that recurrent cholestasis or clinical symptoms can be caused by papillary restenosis which is a known complication of sphincterotomy, usually occurring years after intervention^[31]. We think that the patients' long-term clinical improvement concerning pancreatic pathology is due to a decrease of pancreatic ductal pressure after overcoming the underlying pathogenetic factor of papillary stenosis. Few of our patients (11.7%) reported no improvement or even aggravation in their clinical condition after ES. Most of these cases were classified as chronic pancreatitis III according to the Cambridge-Classification. They showed persisting impaired exocrine pancreatic function after ES indicated by persisting reduced FEC. This sub-group of patients had proven advanced structural and functional abnormalities, which were probably progressive and irreversible. Since pain is often a cardinal symptom of chronic pancreatitis, many studies focus on it beside other clinical symptoms when judging the effect of treatment. This is the first time that the effect of endoscopic sphincterotomy on exocrine pancreatic function based on fecal elastase-1 was investigated. In summary, all patients showed a significant increase in fecal elastase-1 levels after ES, which was even more marked in patients with pathologically low concentrations of fecal elastase-1 prior to ES, indicating that endoscopic sphincterotomy has positive effects on exocrine pancreatic function. A similar effect was found in patients with low, but still normal fecal elastase-1 levels (200-300 µg/g) prior to ES. The results are due to effective treatment of the underlying ethiological factor which leads to normalized ductal pressure of the pancreas and regeneration of pancreatic parenchyma. In

contrast to the common belief of irreversible structural and functional impairment of the pancreas in chronic pancreatitis, the findings of the present study confirm that there is at least a subset of patients with chronic pancreatitis in which a recovery of functional capacity is possible^[32].

In conclusion, patients with stenosis of the ampulla of Vater can be successfully treated with endoscopic sphincterotomy. The positive effect is indicated not only by sustained improvement of biliary type clinical symptoms and laboratory markers of cholestasis, but also by improvement of exocrine pancreatic function and pancreatitis type clinical symptoms. Without question there is a need for prospective, randomized, controlled trials which investigate endoscopic sphincterotomy versus pancreatobiliary stenting and conservative medical therapy in chronic pancreatitis.

COMMENTS

Background

Endoscopic sphincterotomy has been introduced as a treatment for sphincter of Oddi dysfunction. In most recent papers the focus of clinical interest has been put on aspects of cholestasis. In addition to the resulting problems concerning the bile duct system, chronic obstruction of the papilla of Vater may also contribute to lesions of the pancreas, and may also play a role in the pathogenesis of chronic pancreatitis. The aim of this study was to investigate the long-term effects of ES not only on clinical symptoms and parameters of cholestasis, but also on exocrine pancreatic function.

Innovations and breakthroughs

The study showed that patients with stenosis of the ampulla of Vater could be successfully treated with endoscopic sphincterotomy. The positive effect was indicated not only by sustained improvement of biliary type clinical symptoms and laboratory markers of cholestasis, but also by improvement of exocrine pancreatic function and pancreatitis type clinical symptoms. The improvement in exocrine pancreatic function and pancreatic regeneration after endoscopic sphincterotomy is remarkable.

Applications

There is a definite need for prospective, randomized, controlled trials which investigate endoscopic sphincterotomy versus pancreatobiliary stenting and conservative medical therapy in chronic pancreatitis.

Terminology

Sphincter of Oddi dysfunction (SOD): Sphincter of Oddi dysfunction refers to structural or functional disorders involving the sphincter of Oddi that may result in impedance of bile and pancreatic juice flow. Geenen *et al* have divided SOD patients into three types. Type I patients exhibit all three criteria (biliary pain, abnormal liver serology and bile duct dilation). Type II patients have typical biliary pain and either abnormal liver serology or dilation of the bile duct, but not both. In type III patients, the extrahepatic bile duct is not dilated, and abnormal liver serology is not found, whereas pain is present.

Peer review

The authors retrospectively audited a series of 60 patients with stenosis of the ampulla Vater (SOD) who had undergone endoscopic sphincterotomy (ES) and their 3-year follow-up concerning symptom improvement & pancreatic exocrine function. I agree with the acceptance of this manuscript for publication in the WJG.

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