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GIE

GASTROINTESTINAL ENDOSCOPY

Volume 59, No. 7 : June 2004

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A simple way of avoiding post-ERCP pancreatitis

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Background: **Pancreatitis occurs in up to 30% of patients who undergo ERCP. This study tested the hypothesis that post-ERCP pancreatitis can be avoided by initially accessing the bile duct with a soft-tipped Teflon tracer 0.035-inch guidewire.**

Methods: **A single endoscopist performed ERCP in 400 consecutive patients with pancreatobiliary disease who were randomized to two groups. In Group A (200 patients), the bile duct was first accessed by insertion of a soft-tipped Teflon tracer (diameter 0.035 inch) guidewire through a 6F, double channel sphincterotome, followed by cannulation, injection of contrast, and sphincterotomy. In Group B (200 patients), the bile duct was opacified by using traditional methods of cannulation.**

Results: **No case of acute pancreatitis was detected in Group A, whereas, 8 cases were observed in Group B (6 mild, one moderate, one severe) ($p < 0.01$). In 9 patients in Group A vs. 39 in Group B ($p < 0.001$), the serum amylase rose to more than 5 times the upper normal limit during the 24 hours after the procedure. There was no procedure-related mortality.**

Conclusions: **Accessing the bile duct with a soft-tipped tracer guidewire prevents post-ERCP pancreatitis. (Gastrointest Endosc 2004;59:830-4.)**

For many years, endoscopists have studied the problem of post-ERCP pancreatitis, an all to frequent event that is a cause for substantial concern; a recent review of prospective series found the mean frequency to be 5.2% after diagnostic procedures and 4.1% after therapeutic ERCP.[1] In prospective trials, post-ERCP pancreatitis was recorded in 1% to 7% of cases.[2-9] The variation in frequency among studies could be related to differences in the definition of pancreatitis, study populations, and/or techniques. The observed frequency of pancreatitis seems to correlate with the proportion of patients at high risk for the complication, because the rate is higher in series that include large numbers of patients with patient- and technique-related risk factors. Although the frequency of pancreatitis ranges from 1% to 6% in non-selected patients,[6,9-11] it is 12% to 31% in high-risk patients.[6,8,11,12] For this reason, many studies have been performed in an effort to find methods that will decrease the frequency of post-ERCP pancreatitis: use of low-osmolality contrast media[4]; placement of a pancreatic stent after sphincterotomy[11]; improvements in accessory devices, better training of support staff and performance of high-risk procedures only by endoscopists with greater skill and experience (>200 ERCPs per year)[9,13,14]; and administration of pharmacologic agents, such as somatostatin, octreotide, C1-inhibitor, corticosteroids, interleukin 10, glycerol trinitrate, heparin, and gabexate mesilate, before the procedure.[15-23] However, the safety and the effectiveness of these methods remain uncertain.

The present study evaluated the safety and the effectiveness of accessing the bile duct for contrast injection and sphincterotomy with the aid of a guidewire to reduce chemical, traumatic, and other forms of injury to the pancreatic sphincter. This technique was compared with the traditional method of cannulation of the biliary tree (use of a papillotome plus injection of contrast medium).

PATIENTS AND METHODS

From September 2000 to December 2002, 400 consecutive hospitalized patients (182 men, 218 women; mean age 61.2 years, range 22-94 years) who were candidates for ERCP were randomized to two groups (A and B), each with 200 patients, by using random numbers generated by a computer program. In designing the study, a power analysis was conducted for detecting differences at the 5% level of significance between a group with a 5% rate of post-procedure pancreatitis (ERCP performed with standard technique) based on published data and a group with less than a 1% rate of post-procedure pancreatitis (ERCP with guidewire, based on preliminary data). The analysis indicated that a sample with 200 patients in each arm of the study would provide a power of 80%.

Before ERCP, transabdominal US and/or MRCP were performed in all patients. All patients underwent

Received August 7, 2003. For revision December 8, 2003. Accepted February 17, 2004.

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0016-5107/$30.00

PII: S0016-5107(04)00363-3

therapeutic ERCP for biliopancreatic disease: choledocholithiasis (359 patients); biliary malignancy, including hilar tumors and unresectable pancreatic malignancy (24); acute idiopathic recurrent pancreatitis (12); and suspected sphincter of Oddi dysfunction (5) (Table 1). Exclusion criteria were the following: presence of a choledochoduodenal anastomosis, chronic pancreatitis, and previous sphincterotomy. Written informed consent was obtained from all patients, and the study was approved by the ethics committee of our institute.

After an overnight fast, all patients were given standard premedication (pentazocine chloride, 30 mg; hyoscine N-butyl bromide, 20 mg intravenously). Pharyngeal anesthesia was induced with a topical anesthetic. The antibiotic gentamicin was diluted to a concentration of 2 mg/mL in iopamidol (Iopamir; Bracco, Milan, Italy), a low-osmolality contrast medium that was used to opacify the ducts. No drug for the prophylactic prevention of post-ERCP pancreatitis was administered before the procedure. The mean fluid volume given intravenously during the hospital stay before ERCP was about 2000 mL, which was not different between the two groups. ERCP was performed with a standard duodenoscope (ED 3410; Pentax, Hamburg, Germany). All ERCP procedures in both patient groups were performed by the same endoscopist (F.L.). During the 5 years before the study, this endoscopist had performed more than 200 ERCPs per year.

In Group A, a soft-tipped Teflon tracer guidewire, 0.035 inch in diameter (Wilson-Cook Medical Inc., Winston-Salem, N.C.), inserted through a 6F papillotome (Cotton Cannulotome II PC PreCurved Double Lumen Sphincterotome; Wilson-Cook), was used to cannulate the bile duct; after a minimal insertion (1-2 mm) of the papillotome in the papillary orifice, the tracer was advanced under fluoroscopy until it was seen to enter the bile duct. The papillotome was oriented from the 11:00- to the 1:00-o'clock position on the papilla and was bowed to align it correctly with the axis of the bile duct. The guidewire was advanced by light and gradual pressure, with small changes in the degree of bowing and delicate in-and-out movements as necessary. Advancement of the guidewire was controlled by both the endoscopist and the radiologist. As soon as cannulation was obtained, the guidewire was removed to allow injection of contrast medium. Retrograde cholangiography was used for diagnosis and to measure bile duct diameter (at maximum point adjusted for magnification).

In Group B, the standard technique was used for cannulation of the bile duct with a papillotome and injection of contrast medium.

All endoscopic sphincterotomies (EST) in Group A were performed after re-insertion of the guidewire into the bile duct. Before re-introduction of the guidewire, the papillotome was washed with saline solution to clear it of contrast medium. In no patient in Group A was the main pancreatic duct injected. Before ERCP, pancreatic imaging, when necessary, was obtained by MRCP, often with administration of secretin. When EST was required, it was performed in all patients with blend electrosurgical current. The pre-cut technique was not used in any patient.

Table 1. Patient-related risk factors for post-ERCP pancreatitis

Risk factors	Group A	Group B
Age between 18 and 35 years	23	21
History of relapsing pancreatitis	7	5
Previous post-ERCP pancreatitis	3	3
Sphincter of Oddi dysfunction	4	1
Bile duct diameter <8 mm	7	9

Blood oxygen saturation was monitored by using an automated device during all procedures. At the conclusion of each procedure, the endoscopist recorded the details of the maneuvers performed, particularly the ease or the difficulty of cannulation, the number of cannulations, the duration of the procedure, the number of accidental guidewire insertions into the pancreatic duct (for Group A), and the number of pancreatic duct injections (for Group B).

The serum amylase level and the white blood cell count were measured before ERCP and at 2, 4, 8, and 24 hours thereafter. Hyperamylasemia was defined as an increase in serum amylase above the upper normal value (220 IU/L); leukocytosis was defined as a white cell count greater than 10,000 cells/mm^3.[19,24] Pancreatic-like pain was defined as a persistent epigastric pain, often radiating to the back.[24] The presence/absence of pancreatic-like pain was recorded by an endoscopy staff member who was unaware of the serum amylase and white blood cell count values before the procedure and at 2, 4, 8, and 24 hours afterwards. Clinical features considered to be consistent with acute pancreatitis were pancreatic-like pain that persisted for at least 24 hours after the procedure associated with serum amylase levels greater than 5 times the upper normal limit, with or without leukocytosis[6,25]; CT was used to confirm pancreatic inflammation. These features have been proposed by us as the most reliable indicators of post-ERCP pancreatitis.[26,27]

The patient-related factors considered to be associated with a higher risk of post-ERCP pancreatitis for the purposes of the present study were the following: (1) age between 18 and 35 years[5,9]; (2) history of relapsing pancreatitis[5,9]; (3) a previous episode of post-ERCP pancreatitis[9,28]; (4) sphincter of Oddi dysfunction, biliary or pancreatic type,[1,5,9,10] defined, respectively, on the basis of the Milwaukee[29] and Indianapolis classifications[29]; (5) bile duct diameter greater than 8 mm, although it is recognized that available data do not support an increased risk for post-procedure pancreatitis with a non-dilated duct.[1,4,5,29-31] Patients with involvement of the distal biliary tree by malignant strictures were excluded from the evaluation of bile duct diameter. Risk factors for post-ERCP pancreatitis in the two patients groups are shown in Table 1.

Statistical analysis

The occurrence of post-ERCP pancreatitis in the two groups was analyzed with the Fisher exact test. The parameter "hyperamylasemia greater than 5 times the upper normal limit" was evaluated in patients with and without risk factors for post-ERCP pancreatitis, and its occurrence was analyzed by the chi-square test with

Table 2. Risk factors for post-ERCP pancreatitis and frequency of hyperamylasemia greater than five times the upper normal limit

	No risk factors		One or more risk factors	
	Group A	Group B	Group A	Group B
Serum amylase ≤5 times the upper normal	158	131	30	25
Serum amylase >5 times the upper normal	2	18	7	21
	$p < 0.001$		$p = 0.01$	

continuity correction, which also was used for comparisons with the control series of patients. Two-tailed p values were computed.

RESULTS

The bile duct was cannulated in 197 patients in Group A and 195 patients in Group B. Eight procedures (2%) were unsuccessful, 6 because of the presence of a gastroenteric anastomosis that made it impossible to reach the papilla, and two because of neoplastic infiltration of the major papilla.

No episode of acute pancreatitis was detected in Group A, whereas, 8 patients in Group B developed acute pancreatitis after ERCP (difference between proportions 0.51; correlation coefficient 0.14; $p < 0.01$). In 6 cases, the pancreatitis was mild, in one it was moderate, and in one it was severe. For the 6 patients with mild acute pancreatitis, the mean post-procedure hospital stay was 5 days; for the one patient with moderate pancreatitis, discharge occurred 10 days after the procedure, and the one patient with severe pancreatitis remained hospitalized for 1 month, including 15 days in the intensive care unit. There was no procedure-related mortality.

The serum amylase was more than 5 times the upper normal limit during the 24 hours after the procedure in 9 patients in Group A vs. 39 in Group B ($p < 0.01$). These patients remained under observation in hospital until 48 hours after ERCP, whereas, all others were discharged within 24 hours after ERCP. Seven patients in Group A vs. 8 in Group B experienced non-specific abdominal discomfort (mean duration 4 hours) after ERCP that resolved spontaneously or after administration of a single dose of an analgesic drug. As expected, hyperamylasemia (>5 times the upper normal value) was observed more frequently ($p < 0.001$) in patients with one or more risk factors for post-ERCP pancreatitis compared with patients with no risk factor (Table 2).

No patient developed leukocytosis at 24 hours after the procedure. The two groups were well matched in terms of difficult cannulation (42 Group A vs. 48 Group B), number of cannulations (Group A: median 4, range 1-12; Group B: median 4, range 1-15), and median duration of the procedure (37 minutes for Group A vs. 39 minutes for Group B). Accidental insertion of the guidewire into the main pancreatic duct occurred in 82 patients in Group A (median number of insertions 2; range 1-4), but this had no adverse effect. In 113 patients in Group B, contrast was injected unintentionally into the main pancreatic duct, albeit without acinarization. Acute pancreatitis developed in 5 of these patients. In relation to patient-related risk factors, there was no statistically significant difference with respect to the cause of post-ERCP pancreatitis between the two groups.

DISCUSSION

Freeman[32] analyzed post-ERCP complications that occurred during 1 year in the United States in an editorial published in 1998: about 500,000 ERCPs are performed, with an estimated complication rate of 10% (50,000 patients) and a resultant mortality rate of 0.5% (2500 deaths annually). Of these complications, the majority comprised pancreatitis, which also accounts for a substantial proportion of the deaths. The cause of post-ERCP and post-EST pancreatitis is uncertain, and the results of the numerous pertinent studies are still debated. The most common hypotheses are that, during ERCP, the pancreas is subjected to high pressure, infectious, and/or chemical injury after contrast injection, and that it is the target of an acute inflammatory response because of impaired flow of pancreatic juice, repeated cannulation, and/or thermal injury during EST, with resulting papillary edema.[1,5,10,33] For these reasons, some authorities insert a pancreatic stent after ERCP/EST to improve pancreatic flow, and/or to use a low osmolality contrast medium to avoid chemical injury, and to inject the contrast by using low pressure.[4,10,25] The results of these methods have proved insufficient to prevent post-ERCP pancreatitis.

The potential of a number of drugs, such as octreotide, corticosteroids, somatostatin, and gabexate mesilate, administered before ERCP to prevent post-ERCP pancreatitis has been studied.[15-23] The latter protease inhibitor reduces post-procedure hyperamylasemia[34] and pancreatitis[7] but substantially increases the overall cost of ERCP[35]; it must be given as a continuous 12-hour intravenous infusion, which usually necessitates hospitalization and, thereby, makes this agent unsuitable for ERCP in the

outpatient setting. A theoretical economic analysis of the cost-effectiveness and of the cost-benefit ratio of the use of gabexate mesilate to prevent post-ERCP pancreatitis by Atkinson et al.,[36] which assumed an average rate of 2% for post-ERCP pancreatitis (based on data reported for non-selected patients) and efficacy, found that routine prophylactic administration of gabexate mesilate appears to be too expensive.

As outlined above, the use of pharmacologic agents to prevent post-ERCP pancreatitis may be suitable only for patients at high risk for this complication based on patient-related risk factors (small diameter duct, history of post-ERCP pancreatitis or idiopathic recurrent pancreatitis, suspected sphincter of Oddi dysfunction, young age) or procedure-related factors (main pancreatic duct injection and/or pancreatogram, difficult cannulation, pre-cut papillotomy).[9] Although endoscopic expertise is known to influence the outcome of ERCP, it is extremely difficult to evaluate. In a study from Italy, the overall complication rate was closely associated with low case volume (performance of <200 ERCP per year) vs. high volume (7.1% vs. 2.0%).[9] Similarly, a study from the United States published in 1996, found that endoscopists who performed one or fewer sphincterotomies per week had higher overall rates of complications compared with more experienced endoscopists (11.1% vs. 8.4%), particularly severe complications (2.3% vs. 0.9%).[6]

In an effort to reduce the rate of post-ERCP pancreatitis, a prospective study was begun in January 2000, in which 400 consecutive patients undergoing ERCP/EST were randomized to two groups. In Group A, a guidewire was used to access the bile duct and to perform EST, whereas, in Group B, traditional techniques were used. With use of the guidewire technique, which precludes insertion of the papillotome into the pancreatic duct as well as chemical- and pressure-related injury, there was no case of post-ERCP pancreatitis. By contrast, the rate of procedure-related pancreatitis with the standard technique was 4.1%, which is similar to that noted in many studies. As for any comparison trial involving different techniques, there is the possibility that the present study is subject to operator bias, which is unavoidable in this type of investigation. However, the similar rate of successful cannulations in the two groups indirectly confirms that all of the endoscopic procedures were performed with the greatest of care no matter which technique was used.

Guidewire cannulation of the bile duct before contrast injection is a safe and effective method for prevention of post-ERCP pancreatitis. This approach prevents accidental injection of contrast medium into the main pancreatic duct or the papilla itself (submucosal injection) and, thereby, reduces the possibility of chemical- and pressure-related pancreatic injury. Insertion of a double-channel papillotome over the guidewire allows easier and faster cannulation, with little trauma to the papilla, so that the risk of pancreatitis is minimized even in patients at increased risk for this complication. However, the retrospective study of Vandervoort et al.[37] obtained contrary data: guidewire cannulation was associated with a higher rate of post-procedure pancreatitis, albeit only in a univariate analysis. Moreover, in that study, guidewire cannulation was used in a minority of patients, perhaps after standard techniques had failed.

With a guidewire inserted in the bile duct, the safety margin of sphincterotomy improves, because this ensures that the biliary sphincter is incised as intended. Furthermore, the presence of the guidewire facilitates repeated cannulation, which reduces the risk of papillary injury in the event the papillotome becomes dislocated during sphincterotomy. Guidewire cannulation of the bile duct obviates the need for prolonged infusion of pharmacologic agents, thereby, shortening hospital stay and making the technique suitable for outpatients. The results of the present study suggest that routine use of a guidewire to access the bile duct for ERCP could be an effective strategy for avoiding post-ERCP pancreatitis. Based on these results, more extensive study of the efficacy of guidewire access/cannulation for prevention of post-ERCP pancreatitis in larger series of patients is warranted.

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