# Intravenous Synthetic Secretin Reduces the Incidence of Pancreatitis Induced by Endoscopic Retrograde Cholangiopancreatography

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**Objectives:** This study aimed to evaluate whether synthetic secretin is effective in reducing post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

**Methods:** This is a single academic medical center, prospective, randomized, double-blind, placebo-controlled trial using secretin (dose of 16 μg) administered intravenously immediately before ERCP. Patients were evaluated for the primary outcome of post-ERCP pancreatitis as diagnosed by a single investigator.

**Results:** A total of 1100 patients were screened, of whom 869 were randomly assigned to receive secretin (n = 426) or placebo (n = 443) before ERCP and were evaluated after the procedure for efficacy of secretin. The incidence of pancreatitis in the secretin group compared with the placebo group was 36 (8.7%) of 413 patients versus 65 (15.1%) of 431 patients, respectively, $P = 0.004$. In the subgroup analysis, secretin was highly protective against post-ERCP pancreatitis for patients undergoing biliary sphincterotomy (6/129 vs 32/142, $P < 0.001$), patients undergoing cannulation of the common bile duct (26/339 vs 56/342, $P < 0.001$), and patients not undergoing pancreatic sphincterotomy (26/388 vs 57/403, $P = 0.001$). Analysis of the interaction between these groups reveals that the primary effect of secretin prophylaxis was prevention of post-ERCP pancreatitis in patients undergoing biliary sphincterotomy.

**Conclusions:** Synthetic secretin reduces the risk of post-ERCP pancreatitis, particularly in patients in undergoing biliary sphincterotomy.

**Key Words:** post-ERCP pancreatitis, secretin prophylaxis, biliary sphincterotomy, cannulation, pancreatic duct

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Endoscopic retrograde cholangiopancreatography (ERCP) is an important invasive procedure used in managing a diverse group of pancreatic and biliary disorders. The most common serious adverse event is post-ERCP pancreatitis,[1] which can result in significant morbidity and rare mortality. The incidence of this complication varies widely, ranging from 1% to more than 30%.[2–8] There are several likely explanations for this wide variation, as has been discussed previously.[1–12]

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Many strategies have been tried to prevent or reduce the incidence of post-ERCP pancreatitis,[6,13,14] including deferral of ERCP in high-risk patients,[15,16] chemoprophylaxis,[17–26] and periprocedural interventions shown to reduce post-ERCP pancreatitis. In recent years, prophylactic pancreatic stent placement has been used to prevent or reduce the incidence of post-ERCP pancreatitis.[27–29]

Secretin is a gastrointestinal peptide endocrine hormone; its primary function is to stimulate secretion of a bicarbonate-rich fluid from the pancreas. In a retrospective review from our institution, patients who received biologically extracted porcine secretin at the time of ERCP were found to have a significantly lower incidence of post-ERCP pancreatitis than similar patients who did not receive secretin.[30] On the basis of these retrospective data, we performed a prospective, randomized, double-blind, placebo-controlled trial to evaluate the effect of secretin in the prevention of post-ERCP pancreatitis.

## MATERIALS AND METHODS

To test the hypothesis that secretin before duct cannulation would afford protection against post-ERCP pancreatitis, we designed a prospective, randomized, double-blind, placebo-controlled trial conducted at Duke University Medical Center from 1998 to 2001.

Consenting patients 18 years and older scheduled to undergo ERCP were eligible; the physician performing the ERCP also had to assent to the patient's enrollment. The following patients were excluded: ongoing, active acute pancreatitis; known adverse reaction to secretin; initiation of new medication known to cause pancreatitis within 1 month of the procedure; or diagnosis of pancreas divisum. Female patients were excluded if they were pregnant, breast-feeding, or of childbearing potential and not using adequate contraception. Patients undergoing sphincter of Oddi manometry were initially excluded; however, after enrolling 87 patients, we obtained institutional review board (IRB) approval to allow enrollment.

Patients were eligible to enroll in the study more than once if they returned for additional ERCPs. After the completion of the study, the investigators appreciated that this practice introduced an unacceptable bias. Therefore, if a subject was entered more than once, only the initial enrollment was used in the final analysis.

Eligible patients were randomly allocated to receive either synthetic porcine secretin (ChiRhoClin, Inc, Burtonsville, Md) or the same volume of normal saline before attempts at cannulation. Synthetic secretin is identical to biologically derived secretin and has the same pharmacological effects on the exocrine pancreas.[31] Secretin or placebo was administered intravenously before intubating the esophagus. Patients in whom sphincter of Oddi manometry was planned did not receive secretin or placebo until manometry had been completed. The dose

of synthetic secretin was 16 μg (8 mL), which is equivalent to 80 clinical units of biological activity. If the ERCP lasted longer than 30 minutes, an additional 8 μg (4 mL) of synthetic secretin was to be administered. Administering a second dose proved logistically difficult; we therefore reviewed the data after the first 375 patients were enrolled and found that 93 (76%) patients with procedure times longer than 30 minutes were not administered the second dose. We amended the protocol and no additional patients received a second dose. Personnel who prepared study drug were supervised by Duke Research Pharmacy Pharmacists and were not blinded to the randomization; however, the physician and the subject remained blinded. Three (3) physician endoscopists conducted all ERCPs in this study. The 72-hour follow-up evaluation was conducted by a physician blinded to the randomization and not directly or indirectly associated with the endoscopy center personnel and medical staff.

Patients were evaluated before and immediately after ERCP. Before being discharged, they were instructed to contact the investigators to report any adverse postprocedure events. All patients were contacted by telephone 2 to 4 days after their procedure. Before the procedure, patients rated their pain at that moment, as well as for the week before ERCP, according to an ordinal scale where 0 is no pain and 10 is the most severe pain imaginable. At the time of telephone follow-up, patients were again asked to rate pain, nausea, and vomiting on the same 11-point digital scale. Study personnel attempted to review the records of any patients requiring medical attention within 2 days of ERCP.

The primary study end point was post-ERCP pancreatitis, defined as persistent postprocedural pain clinically consistent with pancreatitis. Other studies, including serum amylase, lipase, and abdominal computed tomographic scan, were not routinely obtained but were reviewed whenever available. A single gastroenterologist, experienced in pancreatitis management and blinded to the randomization, reviewed all data. Patients with 1 complaint or more of pain, nausea, or vomiting after procedure were assigned to one of the following categories: (1) pancreatitis, (2) indeterminate for pancreatitis, or (3) not due to pancreatitis. Only patients assigned to the first group were considered to have post-ERCP pancreatitis. When post-ERCP pancreatitis was identified, it was graded as minimal, mild, moderate, or severe (Table 1). Severity was assessed using data from telephone follow-up and reviewing patients' hospitalization records, where available.

## Statistical Analyses

### Power and Interim Analyses

The power calculation was based on the clinical assumption of a 6% incidence of post-ERCP pancreatitis. With a type 1 error of 0.05, approximately 80% power was available to detect a 50% reduction in the rate of post-ERCP pancreatitis in an evaluable sample, defined as having no pancreas divisum, of 749 patients per treatment arm (secretin or placebo).

Because the precise incidence of post-ERCP pancreatitis and the magnitude of reduction in this incidence by secretin were not known, an interim analysis was planned. The original plan was to perform the interim analysis after 50% of patients had completed the study (375 patients per group). If a significant difference in the incidence of post-ERCP pancreatitis ($P \leq 0.01$) was detected between groups, the study was to be terminated. Before the start of the study, the protocol was amended to perform the interim analysis after two-thirds of patients (approximately 1000 of the planned 1500) had completed the study. As noted previously, because of concerns about introducing bias, only data from the initial enrollment were used if a subject had been enrolled more than once. The study protocol, case report form, and all protocol amendments were approved by the IRB (Duke University Medical Center).

### Study Populations

After eliminating 159 instances of multiple enrollment, 18 patients for whom informed consent could not be adequately documented, and 12 patients with pancreas divisum, we obtained a per-protocol randomized population of 911 patients. The "as-treated" population (n = 869) represents patients who received treatment regardless of randomization assignment, but excludes patients reported as being "not administered" (n = 23) or "untreated" (n = 19) per pharmacy logs. In cases where there was a discrepancy between the case report form and pharmacy log, data from the pharmacy log were used. Analysis for the article used the "as-treated" population (see Fig. 1 for study flow).

### Final Analyses

Categorical baseline characteristics and medical history variables were reported using frequencies and percentages; however, no formal statistical comparisons were made. Incidence of post-ERCP pancreatitis was assessed in pancreatitis severity groups as captured in the CRF and defined in the protocol.

Univariate logistic regression was used to compare the efficacy of secretin against placebo for the primary end point of post-ERCP pancreatitis in the intent to treat population (n = 911).

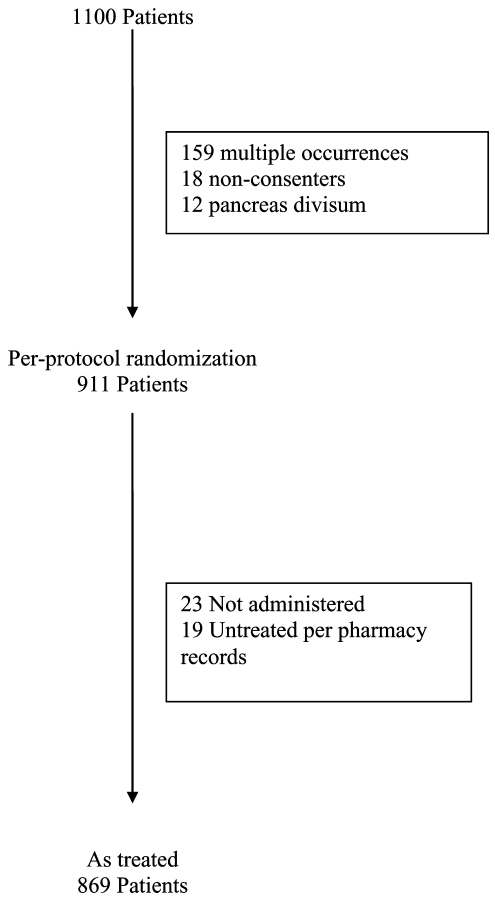


**FIGURE 1.** Study flow.

Although this study was not powered to perform subgroup analyses, the incidence rate of the primary end point of post-ERCP pancreatitis was evaluated on the ITT population within the following a priori subgroups: successful pancreatic duct cannulation, successful common bile duct (CBD) cannulation, biliary sphincterotomy, pancreatic sphincterotomy, bile duct stent insertion, pancreatic duct stent insertion, and stone extraction (balloon or basket). Primary end points were also analyzed on the "as-treated" population within some of the above-defined subsets.

Interactions between treatment and procedural subgroup were tested for statistical significance. If any interaction was detected as statistically significant, logistic regression was used to further analyze the primary end point within the corresponding subgroup(s) and among patients who belonged exclusively to the subgroup(s). Exclusivity of patients within each subgroup was also ensured to accurately interpret results. For example, to test for the interaction between treatment and CBD cannulation, an interaction term was added to the logistic regression model after excluding patients who underwent both CBD cannulation and CBD sphincterotomy.

For all analyses, a 2-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using the SAS System (SAS Institute, Cary, NC).

This study was reviewed and approved by the IRB at Duke University Medical Center.

## RESULTS

The study was conducted between May 11, 1998, and June 5, 2001, at Duke University Medical Center and terminated after the interim analysis because of the finding of a statistically significant efficacy effect. There was no data monitoring committee. A total of 1100 patient procedures were randomized. Distribution of patients across treatment arms was similar for sex, race, age, smoking status, and various procedural aspects of ERCP (Table 2).

The primary end point of post-ERCP pancreatitis was significantly reduced in patients randomly assigned to secretin compared with placebo: 36 (8.7%) of 413 patients versus 65 (15.1%) of 431 patients, $P = 0.004$ (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.35–0.83). Post-ERCP pancreatitis incidence rates at each level of severity by treatment are provided in Table 1.

Incidence of post-ERCP pancreatitis was evaluated in various subpopulations defined by type of procedure performed during ERCP. The terms corresponding to interactions between treatment and procedure subgroups defined by cannulation of PD, stent insertion into CBD, stent insertion into pancreatic duct, and stone extraction were not statistically significant. The interaction terms between treatment and subgroups defined by patients who underwent CBD cannulation, patients who underwent biliary sphincterotomy, and patients who did not undergo pancreatic sphincterotomy were statistically significant ($P = 0.030$, $P = 0.002$, and $P = 0.035$, respectively). The OR (95% CI) for developing post-ERCP pancreatitis within these procedure subgroups of biliary sphincterotomy is 0.17 (0.07–0.42); CBD cannulation, 0.42 (0.26–0.69); and no pancreatic sphincterotomy, 0.44 (0.027–0.71). The ORs and incidence rates by treatment are shown in Figure 2A.

When the effect of biliary sphincterotomy was removed, there was no longer a statistically significant protective effect from secretin for patients undergoing CBD cannulation or for patients in whom no pancreatic sphincterotomy was performed. The ORs for these procedures after excluding the effect of biliary sphincterotomy are the following: CBD cannulation, 0.81 (95% CI, 0.44–1.47); no pancreatic sphincterotomy, 0.74 (95% CI, 0.4–1.36) (Fig. 2B).

**TABLE 1.** Post-ERCP Pancreatitis in Placebo and Secretin Groups According to Severity of Pancreatitis

| | Secretin (n = 413) | Placebo (n = 431) |
|---|---|---|
| Minimal | 13/413 (3.14%) | 20/431 (4.6%) |
| Mild | 11/413 (2.7%) | 21/431 (4.9%) |
| Moderate | 9/413 (2.2%) | 17/431 (3.9%) |
| Severe | 1/413 (0.24%) | 1/431 (0.23%) |

Minimal pancreatitis = pain requiring only outpatient management; mild pancreatitis = pain requiring hospitalization of 1 to 3 days; moderate pancreatitis = pain requiring hospitalization of 4 to 10 days; severe pancreatitis = pain requiring hospitalization more than 10 days, intensive care unit admission, surgery, and/or percutaneous radiological intervention.

**TABLE 2.** Demographic and Procedural Characteristics in Placebo and Secretin Groups

| | Secretin (n = 426) | Placebo (n = 443) |
|---|---|---|
| Sex | | |
| Female | 227/426 (53.3%) | 267/440 (60.7%) |
| Male | 199/426 (46.7%) | 173/440 (39.3%) |
| Race | | |
| White | 346/424 (81.6%) | 353/438 (80.6%) |
| Black | 71/424 (16.7%) | 80/438 (18.3%) |
| Age, mean (SD), yr | 55 (16) | 56 (170) |
| Smoking | | |
| Yes | 136/424 (32.1%) | 111/440 (25.2%) |
| Never | 202/424 (47.6%) | 219/440 (49.8%) |
| Stopped | 86/424 (20.3%) | 110/440 (25.0%) |
| ERCP procedure performed | | |
| CBD cannulation | 366/422 (86.7%) | 382/439 (87.0%) |
| Pancreatic duct cannulation | 253/418 (60.5%) | 272/437 (62.2%) |
| Biliary sphincterotomy | 130/426 (30.5%) | 149/442 (33.7%) |
| Pancreatic sphincterotomy | 25/426 (5.9%) | 28/442 (6.3%) |
| Biliary stent | 91/426 (21.4%) | 102/442 (23.1%) |
| Pancreatic stent | 24/426 (5.6%) | 32/442 (7.2%) |

## DISCUSSION

The pathogenesis of post-ERCP pancreatitis is not fully understood. Potential mechanisms include obstruction at the sphincter of Oddi, increased hydrostatic pressure during contrast injection, activation of pancreatic enzymes, pH of contrast media,[32] and injury during sphincterotomy. The patient group at highest risk are young women with suspected sphincter of Oddi dysfunction, normal bilirubin, and no evidence for chronic pancreatitis.[5,8,10–12,33–35] Procedure-related factors include difficult cannulation, injection of the pancreatic duct, or pancreatic sphincterotomy and dilation of the sphincter of Oddi.[5,7,11,12,36,37]

Avoiding or minimizing technical factors associated with post-ERCP pancreatitis will reduce the risk of this complication. The risk can be even further reduced by placing a pancreatic

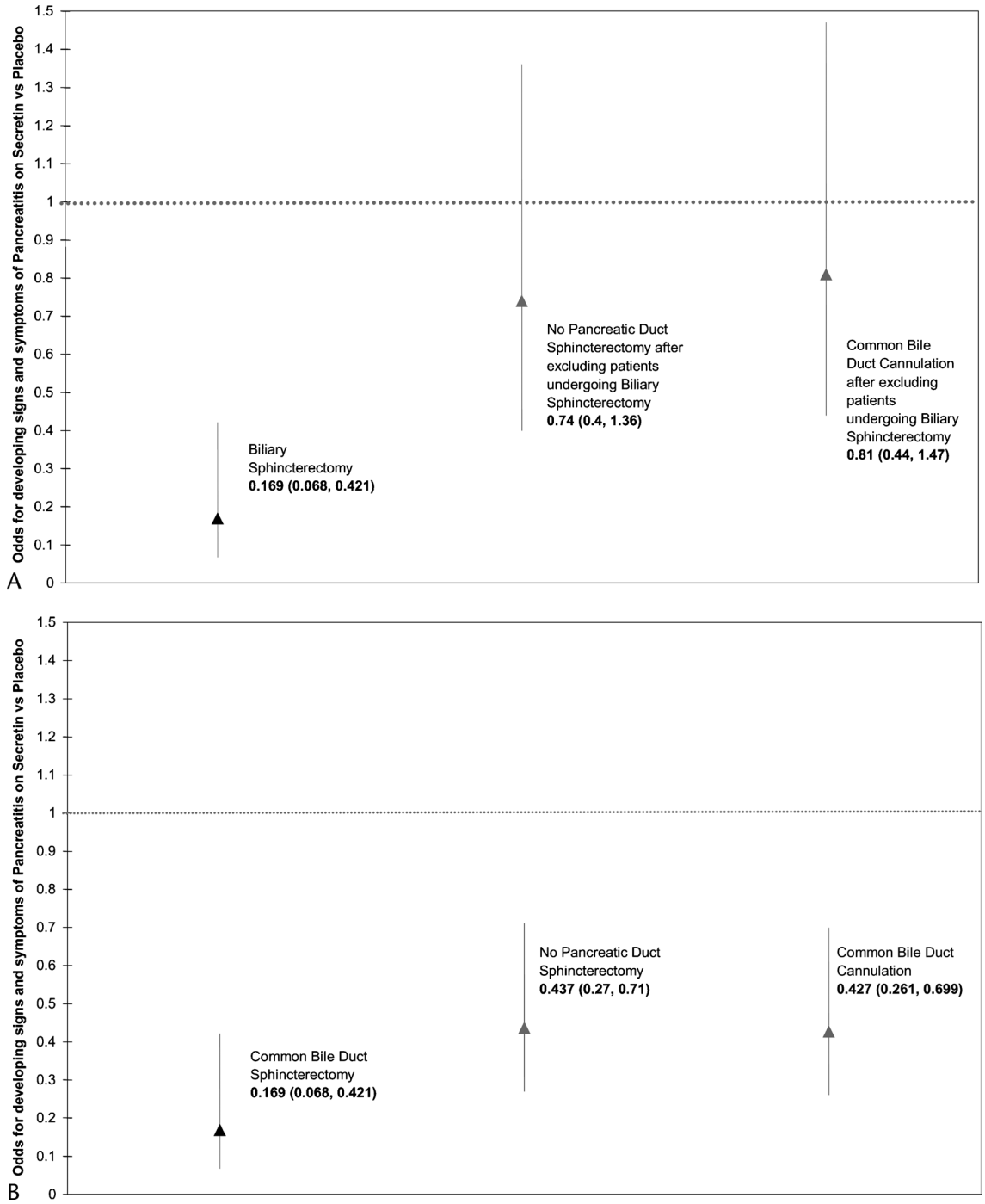


**FIGURE 2.** A, Odds ratios among subgroups for developing pancreatitis. B, Odds ratios among subgroups for developing pancreatitis after excluding patients undergoing biliary sphincterectomy.

stent,[21,35,38–40] an effective technique that was not yet the standard of care at the time our study was conducted.

Pharmacological prophylaxis to reduce risk of post-ERCP pancreatitis is an attractive option. In a randomized controlled trial, gabexate mesilate (FOY) reduced the risk of post-ERCP pancreatitis.[41] However, a recent meta-analysis showed no benefit to gabexate administration.[42] The evidence for nitroglycerine[43,44] initially suggested a possible effect in preventing post-ERCP pancreatitis, but subsequent data have not shown a benefit.[45] Prophylactic treatment with somatostatin[7,42,46–49] or octreotide[50–56] also prompted substantial interest, as initial studies showed that somatostatin might prevent post-ERCP pancreatitis. However, 1 meta-analysis indicated that octreotide is ineffective at preventing post-ERCP pancreatitis,[57] and a more recent meta-analysis indicated that somatostatin does not protect against post-ERCP pancreatitis.[42] Several studies have shown an *increase* in post-ERCP pancreatitis in patients who received octreotide[52,55]; this may be due to octreotide's

 

propensity to increase sphincter pressure.[58] Other agents that have failed to demonstrate any protective effect include calcium channel blockers, heparin, and corticosteroids.[6] As can be appreciated, the plethora of studies reflects the lack of efficacy of any of these agents.[59]

Our study is the first randomized trial to evaluate secretin as chemoprophylaxis for post-ERCP pancreatitis. Our findings show that the administration of intravenous secretin before cannulation results in a significant decrease in the incidence of post-ERCP pancreatitis, which occurred in 8.7% of patients receiving secretin, compared with 15.1% who received placebo. The initial a priori power calculation indicated that 1500 patients would be needed, with an interim analysis planned after two-thirds of patients had been enrolled. A statistically significant decrease ($P = 0.004$) in incidence of post-ERCP pancreatitis was detected at the time of the interim analysis, and the study was terminated.

Subgroup analysis showed a very strong protective effect of secretin for patients who had undergone biliary sphincterotomy: post-ERCP pancreatitis occurred in 4.7% of patients receiving secretin compared with 22.5% of those receiving placebo ($P < 0.001$). If CBD cannulation was performed, the risk of post-ERCP pancreatitis was 7.7% in the secretin group and 16.4% in the placebo group ($P < 0.001$). A statistically significant reduction in post-ERCP pancreatitis was also observed in patients who received secretin but did not undergo pancreatic sphincterotomy; however, when the protective effect of biliary sphincterotomy was excluded from the biliary cannulation group and from the group of patients who did not undergo pancreatic sphincterotomy, no protective effect was detected. Thus, the primary effect of secretin in preventing post-ERCP pancreatitis was in patients who underwent biliary sphincterotomy.

The incidence of post-ERCP pancreatitis in the placebo group was 15.1% higher than incidences reported in many studies. There are several possible explanations. All study patients who were included in the final analysis were followed to determine whether post-ERCP pancreatitis occurred. Most studies published to date did not use such close follow-up; it is possible that by contacting all patients after discharge, we identified instances of post-ERCP pancreatitis that would have been missed with less rigorous follow-up.

The definition of post-ERCP pancreatitis used in our study may also have contributed to the high rate of this end point observed among the placebo group. Our definition did not mandate serum amylase and/or lipase estimation or abdominal computed tomographic scanning in all patients because post-ERCP pain, nausea, and/or vomiting were managed symptomatically; hence, some patients may have had post-ERCP pain that was not due to pancreatitis. To assess the impact of post-ERCP pancreatitis, we assigned each episode into 1 of 5 categories (Table 2). The numerical trend was consistent in favoring a protective effect of secretin administration across all severities. Also, most patients who developed post-ERCP pancreatitis required hospitalization (62% in the secretin group and 66% in the placebo group). Therefore, even if some of these patients did not have post-ERCP pancreatitis, their pain was sufficiently severe to require hospital admission for the majority. If part of the protective effect of secretin was to reduce pain (even if not due to pancreatitis) and thereby hospitalization, this would remain a clinically relevant benefit.

Post-ERCP pancreatitis occurs in a relatively small percentage of all patients undergoing ERCP. Routine use of secretin before every ERCP cannot be recommended on the basis of our data. However, targeted use of secretin in high-risk populations, such as young women, patients undergoing biliary sphincterotomy, and patients with a history of post-ERCP pancreatitis, should be considered. Pancreatic stent placement was not routinely performed for post-ERCP pancreatitis prophylaxis in high-risk patients during the period our study was conducted. It is not clear how the current practice of pancreatic stent placement in many patients undergoing ERCP would affect the benefit of secretin administration seen in this study. Questions of cost-effectiveness should also be evaluated—additional cost of secretin to ERCP; how this compares with the cost of stent placement as well as stent follow-up procedures is unknown but important.

In summary, this study showed that prophylaxis with synthetic secretin significantly reduced the risk of post-ERCP pancreatitis in certain subgroups, particularly those who underwent biliary sphincterotomy. These results support using secretin before many ERCPs. However, when considering costs and the competing technique of prophylactic pancreatic stent placement, the role of secretin in the prevention of post-ERCP pancreatitis is less clear. Presently, the US Food and Drug Administration–approved (May 18, 2006) Special Protocol Assessment based on this study for the prevention of post-ERCP pancreatitis did not consider prophylactic pancreatic stent placement. Further evaluation of secretin, possibly in head-to-head comparisons with pancreatic stent placement in high-risk patients, is warranted to explore further means of reducing the risk of post-ERCP pancreatitis.

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