Post-ERCP pancreatitis: Can synthetic secretin lead to a refractory period were ERCP is relatively safer? A prospective, double-blinded randomized trial.

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A. Study purpose and Rationale

Endoscopic Retrograde Cholangiopancreatography (ERCP) and related therapeutic procedures are widely performed, but complications are relatively frequent, among which clinical pancreatitis is the most common. The overall frequency varies among studies. The highest has been reported in prospective studies with strict diagnostic criteria with the frequency ranging from 1% to 40%. In retrospective studies the average is 1% to 7%, and, in spite of its generally benign course, hospitalization of several days duration is required. (1,2) Factors that likely affect the varying rate of post procedure pancreatitis include different criteria for defining pancreatitis, differing methods of data collection, and differences in patient population.

While the majority of cases of post-ERCP pancreatitis are mild (about 90%) with only 1-2 days of hospitalization followed by full recovery, the remainder may develop severe pancreatitis and have a significant morbidity and mortality. They can require prolonged hospitalization, ICU stay, and utilization of major hospital resources. (1,2) Furthermore, despite increased experience and technical advances, the incidence of post-ERCP pancreatitis has not declined in recent years. (2)

Investigators have been searching for a pharmacologic agent and additional strategies that would prevent or limit the severity of post-ERCP pancreatitis, however, most studies have not yet yielded a proven method. Trans-sphincteric pancreatic stent placement has become an increasingly popular approach. Their mechanism of action is not clearly understood. In theory, the stents preserve flow of pancreatic juice after instrumentation and empty the gland of reactive enzymes. Several studies have found a statistically significant lower rate of post-ERCP pancreatitis in patients with pancreatic stent placement. (1, 3) A meta-analysis of 5 prospective studies (4 randomized, 1 non-randomized) demonstrated the odds ratio of post-ERCP pancreatitis without stent was 3-fold higher than that with stent. (3)The major caveats to pancreatic stent placement includes failure rate for placement (about 5-10% at centers of expertise), accidental placement of stent entirely within the duct, migration of stent inward, and ductal perforation by stent. (1) Furthermore, patients with stent placement require follow-up to ensure passage of the stent and if the stent has been retained, would require a second endoscopic procedure for removal, thereby increasing the overall cost of treatment. (4)

Several pharmacologic substances have been investigated in an attempt to prevent post-ERCP pancreatitis. Most research has aimed at interrupting possible mechanisms of injury such as trauma to the pancreatic sphincter with obstruction of secretions, acinar toxicity induced by contrast media, and inhibiting the inflammatory cascade. Nifedipine which decreases the basal pressure of the sphincter of Oddi, lowers the amplitude of sphincter contractions, shortens the duration and decreases the frequency of contractions was ineffective in two randomized control trials. (1,5) Given that inflammatory cytokines are released during acute pancreatitis, Interleukin 10 (IL-10) a potent anti-inflammatory cytokine with immunosuppressive and anti-inflammatory activities has been studied for prophylactic immunomodulation of the pro-inflammatory cascade. However, randomized trials demonstrated that it was not effective in reducing the incidence or severity of ERCP-induced pancreatitis. (6) Gabexate mesilate is a protease inhibitor studied in the prevention of post-ERCP pancreatitis. A meta-analysis found it to be barely effective with a NNT of 35 to prevent pancreatitis. Further limitations include an infusion time of at least 12 hours and it is currently not available in the U.S. (7) Somatostatin, inhibits acinar secretion, and despite many studies, its use still remains controversial with some studies demonstrating it to be efficacious and others to be ineffective. (1, 8, 9, 10) In addition, it is also not

available in the U.S. Octreotide is a pancreatic anti-secretory agent available in the U.S. Most studies have shown octreotide to be ineffective at preventing post-ERCP pancreatitis. (1, 11)

Multivariate analyses have elucidated some patient characteristics that may be risk factors for post-ERCP pancreatitis. Sphincter of oddi dysfunction, history of post-ERCP pancreatitis and young age have been found to be significant risk factors that can increase the risk of developing pancreatitis. (12)

Given the overall morbidity and mortality of post-ERCP pancreatitis, further studies are needed to explore other pharmacological options that can limit or prevent this complication. Synthetic porcine secretin is a pure peptide hormone drug product with an amino acid sequence identical to naturally occurring secretin. Secretin injections are FDA approved for use as *in vivo* diagnostic agents for pancreatic function and for the diagnosis of gastrinoma. The primary action of secretin is to increase the volume and bicarbonate content of secreted pancreatic juices. The elimination half-life of synthetic secretin is about 27 minutes. (13)

a. Study Question: An IV injection of synthetic secretin, a gut hormone, causes a rapid outpouring of bicarbonate-rich fluid from the exocrine pancreas. Can giving secretin an hour prior to ERCP empty the pancreas of stored proteases and increase bicarbonate secretion leading to a refractory period were ERCP is relatively safer?

B. Study Design and Statistical Analysis

The study will be a randomized, prospective, double-blinded, placebo-controlled clinical trial to be carried out in about 1000 consecutive patients undergoing diagnostic or therapeutic ERCP. Approval by the hospital's institutional review board will be obtained. Informed consent will be obtained at the time of study enrollment.

All study patients will be randomized to receive either placebo or treatment with intravenous bolus secretin 1 hour prior to ERCP. Randomization as well as medication packaging and dispensing in a double-blinded fashion will be performed by the research pharmacy at the university-affiliated medical center.

Study subjects will be risk-stratified according to age, suspected sphincter of Oddi dysfunction, therapeutic versus diagnostic ERCP and history of post ERCP pancreatitis prior to randomization. To design a study with a power of 80% and alpha value of 0.05 would require approximately 1000 patients. Therefore, the study will include about 1000 patients and will have 80 percent power to detect a 50% relative reduction in risk. The smallest difference (or treatment effect) of clinical interest was chosen to be a relative risk reduction of 50% (i.e. 10% -> 5%). The power analysis demonstrated the average number of patients in the study should be about 1000, with approximately 500 patients being randomized to each study arm. This calculation is based on the assumption of a 10% mean incidence of acute pancreatitis in the placebo group and a mean relative risk-reducing effect of 50% in the secretin group.

Categorical variables will be reported as the percentage frequency of occurrence. Continuous data will be presented as means standard deviations (SD). Ninety-five percent confidence intervals will be reported for the primary outcome, the occurrence of acute pancreatitis. The results will be analyzed by the Chi-square test and a multiple logistic regression analysis will also performed to calculate the odds ratio for the occurrence of post-ERCP hyperamylasemia and post-ERCP pancreatitis. Analysis will be on an intention to treat basis.

C. Study Procedure

ERCP is diagnostic test used to examine the duodenum (the first portion of the small intestine), the bile ducts, the gallbladder and the pancreatic duct. A long, flexible, viewing instrument (a duodenoscope) about the diameter of a pen is used to perform the ERCP. The duodenoscope is flexible and can be directed around the many bends of the stomach and intestine. The throat is anesthetized with a spray or solution, and the patient is usually mildly sedated. The duodenoscope is then inserted through the mouth, to the back of the throat, down the food pipe, through the stomach and into the first portion of the

small intestine (duodenum). There is a small opening in the duodenum, named the papilla of Vater, through which a small plastic catheter (cannula) is passed through an open channel of the duodenoscope and into the bile ducts and/or the pancreatic duct. Contrast material (dye) can then be injected and x-rays can be taken of the bile ducts and the pancreatic duct. An exam usually takes between 20 and 40 minutes. Most ERCPs are done on an outpatient basis.

The 1000 study patients would be recruited serially as they present for diagnostic or therapeutic ERCP if they did not meet any of the exclusion criteria (see below). Overall length of study will be approximately 2 years to enroll 1000 patients. Before undergoing ERCP, all patients would receive sedation and prophylactic antibiotic administration. The same contrast medium would be used in all patients. All patients will need to fast for 12 h before and at least 8 h after the procedure, and all will need to stay in hospital at least 24 h after ERCP. Patients will be assessed clinically for pain and serum amylase levels will be measured at time 0, prior to receiving placebo or secretin, then again at 3, 8, and 24 hours after the procedure.

The patients would be randomly assigned into two groups: placebo versus bolus secretin in a blinded fashion by pharmacy staff by using random computer generated numbers. Envelopes that concealed the randomization to active drug or placebo would be dispensed. Nurses who administer sedation and monitor the vital signs of the patients would not know to which group patients had been randomized. The placebo group would receive an intravenous "test dose" of normal saline followed by observation for 1 minute. Then a bolus normal saline intravenous injection would be given 1 hour prior to the procedure. The secretin group would receive an intravenous test dose of 0.2 mcg and observed for 1 minute. If no allergic reaction is noted after 1 minute, the full dose of synthetic porcine secretin (0.2 μg/kg) can administered 1 hour prior to procedure.

Ultrasonography will be performed in cases with 24-h hyperamylasemia more than five times the normal upper limit, and/or pain. If there is suspicion of pancreatic focal necrosis and pancreatic or peripancreatic fluid collections are suspected on ultrasonographic examination, these patients will further undergo abdominal computed tomography (CT scan).

Patients with post-ERCP pancreatitis will be followed until recovery from the complication.

The ERCP findings, patients' clinical characteristics (demographics, reasons for endoscopic examination, indication for procedure), specific endoscopic interventions (sphincterotomy, precutting, stone extraction, stent placement), difficulty of cannulation, number of injections of the pancreatic duct, and degree of duct injection (opacification of primary or secondary main pancreatic duct branches or acinarization), anatomical aspects (major papilla, descending duodenum, biliary tree and pancreatic ductal system), will be recorded by the endoscopist and confirmed by the assisting GI fellow.

The primary objective of this study is to analyze the occurrence of acute pancreatitis. Secondary objectives are length of hospital stay, death, and the frequency and degree of hyperamylasemia after ERCP. Severity of pancreatitis will be measured by the duration of hospitalization. The safety of the treatment including adverse effects reported by the patients and/or recorded by attending physicians will also be assessed.

Definitions

We will consider the following patient-related factors to be associated with a higher risk of post-ERCP pancreatitis: (a) age between 18 and 35 years (b) previous episode of post-ERCP pancreatitis, defined as persisting 24-h post-procedure pancreatic-like pain, with at least a threefold increase in serum amylase (c) sphincter of Oddi dysfunction, biliary and pancreatic type, defined on the basis of the Milwaukee and Indianapolis classifications, respectively, and diagnosed on the basis of radiological and clinical findings in type 1 dysfunction, confirmed by manometric investigation in types 2 and 3. (11)

Hyperamylasemia will be defined as an elevation of serum amylase level above the upper limit of normal if the baseline level is within the normal range, or any further elevation if the baseline level exceeds the normal value.

ERCP-induced pancreatitis will be defined based on Cotton's consensus criteria as the combination of new or worse, severe and persistent, and epigastric or periumbilical pain associated with

serum amylase greater than 3 times the upper limit of normal that required hospitalization for more than 24 hours after the procedure. (14)

The difficulty of cannulation will be defined by the number of attempts at insertion of the cannula into the papilla and graded as easy (<5 attempts), moderate (6-15), and difficult (>15 attempts). (15) ERCP will be defined as therapeutic when endoscopic sphincterotomy, biliary drainage, or both were carried out.

D. Study Drug:

Synthetic porcine secretin is a pure peptide hormone drug product with an amino acid sequence identical to naturally occurring secretin. Secretin injections are FDA approved for use as *in vivo* diagnostic agents for pancreatic function and for the diagnosis of gastrinoma. The primary action of secretin is to increase the volume and bicarbonate content of secreted pancreatic juices. The elimination half-life of synthetic secretin is about 27 minutes. (13) An intravenous test dose of 0.2 mcg is given and the patient is observed for 1 minute. If no allergic reaction is noted after 1 minute, the full dose of synthetic porcine secretin (0.2 µg/kg) can be administered, as is standard use. Occasional mild adverse events were noted in association with the use of synthetic porcine secretin in clinical studies of over 556 patients and 24 volunteer subjects.

Adverse Events

Event	SecreFlo N = 556 Incidence (Patients)
Abdominal cramps	1 (1)
Abdominal discomfort	6 (5)
Bleeding-sphincterectomy	2 (2)
Bleeding-upper GI 2° to endoscopic abrasion	1 (1)
Bloating	1 (1)
Bradycardia (mild)	2 (2)
Decreased blood pressure	2 (2)
Diaphoresis	2 (2)
Diarrhea	1 (1)
Endoscopic perforation of pancreatic duct	2 (2)
Fever	1 (1)
Nausea	5 (5)
Transient low O^2 saturation	1 (1)
Transient respiratory distress	1 (1)
Urticaria 2° contrast material (prior to secretin administration)	1 (1)
Vomiting	1 (1)
Total patients with AEs (%)	29 (5.2)

taken from www.fda.gov/cder/foi/label/2002/21136lbl.pdf

E. Medical Device

No medical devices will be used in this study.

F. Study Questionnaires

No study questionnaires will be used in this study.

G. Study Subjects

Patients presenting for diagnostic or therapeutic ERCP who do not meet the following exclusion criteria: (1) age less than 18 years, (2) pregnancy or lactation (3) chronic renal failure (4) acute myocardial infarction during the last 3 months before the procedure (5) known allergy to secretin (6) acute pancreatitis in patients undergoing early ERCP in the acute phase (7) planned biliary stent removal or exchange without pancreatogram (8) history of alcohol or drug abuse (9) recent use of narcotic analgesics or anticholinergic medications (10) history of chronic pancreatitis, or other diseases known to effect pancreatic secretion (vagotomy, gastrectomy, inflammatory (11) refusal to participate.

H. Recruitment of Subjects

All patients presenting for diagnostic or therapeutic ERCP to the gastroenterology endoscopy department at Columbia University Medical Center without the above exclusion criteria will be considered for inclusion in the study. Risks, benefits, and details of study will be explained and written informed consent obtained for participation in the study. Patients registered in study are not able to participate in other clinical studies.

I. Confidentiality of Study Data

Patient confidentiality will be in strict adherence with HIPAA regulations. The data obtained for this study will track each subject by a unique, confidential numeric identification code. Investigators will remove all other patient identifying information from all records maintained for the purpose of this study. All practices will be in accordance with IRB regulations.

J. Potential Conflict of Interest

None

K. Location of Study

Columbia University Medical Center Department of Gastroenterology Endoscopy Suite.

L. Potential Risks

Potential risks to the patient would be those listed above as the possible adverse events of receiving synthetic porcine secretin.

M. Potential Benefits

Establishing an additional therapy to prevent or limit post-ERCP induced pancreatitis.

N. Alternative Therapies

The alternative to participating in this study would be to not participate and undergo standard of care ERCP.

O. Compensation to Subjects

Subjects will be compensated $30 for the 24 hours post procedure hospitalization that is a requirement of the study which is not standard of care.

P. Costs to Subjects

There will be no additional costs to subjects. Additional studies such as ultrasound and CT scans would be covered by insurance as standard of care for a patient post-ERCP that has developed abdominal pain and hyperamylasemia.

Q. Minors as Research Subjects

There will be no minors enrolled in this study.

R. Radiation or Radioactive Substances

The ERCP procedure requires the use of fluoroscopy to visualize the pancreatic duct and biliary ducts. Patients undergoing a standard ERCP would still be exposed to the radiation required for fluoroscopy.

S. References

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