Exit Examination

Gastroenterology & Hepatology

Title

Somatostatin in the prevention of post ERCP Pancreatitis

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Content

Abstract

Background: Acute pancreatitis is the most common complication after ERCP. Prophylactic somatostatin infusion has been demonstrated to reduce the incidence of post ERCP pancreatitis. However, the cost for continuous intravenous infusion and in-patient treatment to deliver somatostatin is high. Bolus somatostatin injection has also been shown to inhibit pancreatic exocrine secretion and reduce the incidence of post ERCP pancreatitis.

Aim: The aim of this study was to see if bolus somatostatin injection could prevent post ERCP pancreatitis in our local population. Possible patient and procedure related risk factors for post ERCP pancreatitis were also studied.

Patient and methods: A single centred, randomized, double-blind, placebo controlled, prospective study was carried out in patients undergoing diagnostic +/- therapeutic ERCP. Patients were randomized to receive bolus injection of 250mcg somatostatin (group A) or the same volume of normal saline injection as placebo (group B) just before the cannulation of the papilla. The incidence of pancreatitis was compared between the two groups by Fisher's Exact test. Possible risk factors were identified by comparing patients with or without pancreatitis using student t-test, chi square test (or Fisher's Exact test), or Mann Whitney test. Independent risk factors were then identified by backward stepwise multiple logistic regression.

Results: From 8/1/1999 to 13/2/2001, 160 patients were recruited for study with 80 patients in each group. Mean age of patients was 58 $\pm$ 14, with a male to female ratio of 1.3: 1. 10 patients (6.3%) developed post ERCP pancreatitis, 4 patients (5%) in the somatostatin group (3 mild and 1 moderately severe) and 6 patients (7.5%) in the placebo group (5 mild and 1 moderately severe). The difference did not reach statistical significance (P=0.75). All pancreatitis were self-limiting and uncomplicated.

120 patients (75%) developed hyperamylasemia. There was no significant difference between the two groups in terms of the incidence of hyperamylasemia (P=0.72), significant hyperamylasemia (amylase >3x ULN) (P=0.41), mean amylase level at 4 hours (P=0.51) and 18 hours (P=0.53) after ERCP, and persistent abdominal pain (P=1.0).

Longer procedure time (P=0.002), difficult selective biliary cannulation (P=0.016), multiple pancreatic duct cannulation (P=0.024), secondary or higher degree of opacification of pancreatic duct (P=0.035) were associated with post ERCP pancreatitis in univariate analysis. Longer procedure time was found to be the only independent risk factor for post ERCP pancreatitis in multivariate model. Therapeutic procedures performed in the study (papillotomy, stone extraction, biliary stenting, cytology brushings) were not associated with increased post ERCP pancreatitis (P=0.319)

Conclusion: Prophylactic bolus somatostatin injection did not significantly reduce the incidence of post ERCP pancreatitis in unselected patients. Longer procedure time, difficult selective biliary cannulation, increased number of pancreatic duct cannulation, and secondary

or higher degree of opacification of pancreatic duct were associated with increased risk of post ERCP pancreatitis. Only longer procedure time was found to be an independent risk factor for post ERCP pancreatitis.

Introduction

With the improvement in technology, instruments and techniques, ERCP has evolved from purely a diagnostic study to providing a variety of therapeutic modalities. However, it is not without risk, especially many more invasive procedures are now being performed (1).

Subclinical pancreatic injury signified by isolated raised pancreatic enzymes is very common after ERCP. The incidence of hyperamylasemia ranged from 44% to 94% (2-6). Pancreatitis is the most common complication of ERCP, with the incidence ranging from 2.8% to 10.2% in recent, large prospective studies (7-10). A recent prospective study on somatostatin infusion in prevention of post ERCP pancreatitis in Hong Kong (11) revealed an incidence of pancreatitis of 10% in the placebo group. In a large clinical audit on ERCP, M.L. Szeto et al. (12) retrospectively reviewed 732 ERCPs from 13 hospitals in Hong Kong and found an incidence of post ERCP pancreatitis of 1.4%.

Although clinical pancreatitis after ERCP is usually mild and self-limiting, it still incurs significant morbidity in terms of abdominal pain and prolonged hospitalization. It becomes clinically even more important in severe cases, when pancreatic necrosis, secondary infection with abscess formation, systemic multi-organ failure occur. Even deaths have been reported. A study on major complications of ERCP noted moderate to severe pancreatitis in 1.3% of patients (13). Two recent studies by M.L. Freeman et al. revealed that the incidence of severe pancreatitis was 0.4% and 0.3% for biliary sphincterotomy (14) and ERCP (10) respectively. Two United States centres retrospectively reviewed more than seven thousand five hundred cases of ERCP (15). They found an incidence of 0.5% and 1% for severe complications and a death rate of 0.07% and 0.11% for diagnostic and therapeutic ERCP respectively. Besides causing significant morbidity and mortality to patients, there can also be potential medico-legal consequences. A study on malpractice claims in gastrointestinal endoscopy in United States (16) revealed that 1.8% of claims were related to ERCP. The relative risk of claims for ERCP was 1.6 when compared to sigmoidoscopy, which was ranked second after colonoscopy (relative risk 1.7).

Treatment, or preferably, prevention of post ERCP pancreatitis is therefore clinically important. Unfortunately, medical therapy for acute pancreatitis has not been promising and treatment at present is mainly supportive. Lexipafant, a platelet activating factor antagonist, has been studied for treatment of acute non-iatrogenic pancreatitis. But results were disappointing (17). Somatostatin and its analogues have shown some evidence of reducing the severity of pancreatitis in animal (18) and human studies (19). But the effect is, expectedly, difficult to be elicited because the drug is usually given late in the course of the disease when the cascade of

systemic inflammatory response has already been triggered. Thus, a search for effective therapy that can prevent post ERCP pancreatitis is imminent.

Prophylactic somatostatin bolus injection has been shown in previous studies to protect against post ERCP pancreatitis (20) and reduce enzyme elevation (4,20). It works by minimizing pancreatic acinar injury through inhibition of pancreatic enzyme production (21). Its effect on relaxation of the sphincter of Oddi (22) may also help reduce the risk of post ERCP pancreatitis, possibly by allowing easier cannulation, reduction of pressure in the pancreatic duct, improved drainage of contrast and activated pancreatic enzymes. Although the plasma level of somatostatin is short in half-life, its effect on the pancreas may last longer. Pancreatic secretion remains reduced for more than ten minutes after a bolus injection of somatostatin (20). Prophylactic somatostatin infusion has also been demonstrated in a prospective, randomized, placebo controlled study to reduce incidence of post-ERCP pancreatitis from 10% to 3% (11). However, a bolus dose rather than continuous infusion would be more advantageous in reducing drug costs and in obviating the need for hospital stay for drug treatment.

This prospective study would like to address the question whether a bolus dose of somatostatin can reduce the incidence of post ERCP pancreatitis in our local population. Various possible risk factors associated with post ERCP pancreatitis were also studied.

Patient and methods

Starting from 8/1/1999, all patients undergoing ERCP would be eligible.
Exclusion criteria were as follows:

1) age <18 or >80
2) history of allergy to somatostatin
3) pregnancy
4) serious medical disorders
5) previous papillotomy
6) acute pancreatitis*

*Patients with acute pancreatitis after the acute stage were also included into the study provided that they had no more abdominal pain and their amylase level normalised before the study.

Informed written consent was obtained from patient. The study was approved by the hospital ethics committee. The drugs were supplied by the Serono Pharmaceutical Company.

Patients were randomised into group A: receiving intravenously bolus somatostatin 250mcg just before cannulation of the major papilla, or group B: same amount of normal saline intravenously as placebo. Patients, doctors and nurses in the endoscopy suite were blinded to the drug given. The drugs were prepared into unlabelled identical syringes outside the endoscopy suite. By opening sealed envelopes, which contained information on randomised treatment arm to be allocated, the corresponding medication was prepared.

Patients were kept fast for at least 6 hours before ERCP. They were given pharyngeal anesthesia with xylocaine and conscious sedation with intravenous diazemuls and pethidine. Intravenous ciprofloxacin 200mg was given as prophylactic antibiotic for patients with obstructive jaundice. ERCP were performed by trainees in gastroenterology under supervision or by experienced endoscopists themselves. Pancreatic duct cannulation was not routinely performed unless clinically indicated. Conray (Meglumine lothalamate 60%), a high osmolality ionic contrast, was used for opacification. Papillotomy, if required, was performed using a blended current.

The number of pancreatic duct cannulation and pancreatic duct injection, the degree and extent of pancreatic duct opacification was recorded. The number of pancreatic duct injection referred to the number of times any volume of contrast was injected into the pancreatic duct. The degree was graded as primary if only the main pancreatic duct was shown, as secondary if pancreatic side ducts were shown, or as acinarization if any focal or diffuse parenchymal blush

was shown. The extent was graded as 1 if opacification was only up to the head of pancreas, as 2 if opacification was up to the body, as 3 if the whole pancreatic duct was opacified. The difficulty of selective biliary cannulation was graded as easy or difficult by the endoscopist. Failed cases were considered as difficult. The indications for ERCP, bilirubin level before ERCP, ERCP diagnoses, therapeutic procedures and procedure time were also recorded. The procedure time was measured from the commencement of papilla cannulation to the time of withdrawal of endoscope from the patient.

Serum amylase levels were checked before ERCP, 4 hours and 18 hours after ERCP. Lipase measurement was not available in our hospital. Patients were assessed by endoscopists before ERCP for obtaining consent and examine for abdominal signs. They were reassessed 4 hours and 18 hours after the procedure for abdominal pain, the need for analgesia, and complications. Hyperamylasemia was defined as amylase level above the upper limit of normal. Significant hyperamylasemia was defined as amylase level more than 3 times above the upper limit of normal. Persistent abdominal pain was defined as new onset abdominal pain that persisted till 18 hours after ERCP. Pancreatitis was defined as significant hyperamylasemia in the presence of persistent abdominal pain (i.e. new onset abdominal pain after ERCP that persisted till 18 hours after ERCP with a rise in amylase level to more than 3 times the upper limit of normal.) (20).

The severity of pancreatitis was graded according to the consensus criteria in 1991(23): mild if prolonged hospitalisation for <4 days; moderate if prolonged hospitalisation for 4-10 days; severe if prolonged hospitalisation for >10 days, or haemorrhagic pancreatitis, or complications like pseudocyst, abscess, or intervention required (percutaneous drainage or surgery), or the patient died.

Statistical analysis

Numerical data were expressed as mean $\pm$ standard deviation. Amylase levels were compared by student t-test. Frequency of pancreatitis, hyperamylasemia, and persistent abdominal pain were compared by chi-square test (or Fisher's exact test if appropriate). Risk factors for pancreatitis were identified in univariate analysis by Student t-test for numerical variables, chi-square test for nominal variables, and Mann Whitney test for ordinal variables. Significant factors noted in univariate analysis were then included in a backward stepwise multiple logistic regression to identify independent risk factors. A P-value of 0.05 was considered statistically significant (2-tailed).

Results

From 8/1/1999 to 13/2/2001, 451 ERCPs were performed. Many patients were excluded because of previous papillotomy, consent not obtainable, or refusal to enter into study. A total of 161 patients were recruited for study. One patient was excluded from the study because the correct medication was not given according to the information provided in the envelope.

Demographic data:

The mean age was 58 $\pm$ 14, range (28-80). Male to female ratio was 1.3: 1 (90/70). The age, sex, indications for ERCP, patients with raised bilirubin level, the endoscopic diagnoses, the number of diagnostic and therapeutic ERCP, and the procedure time were all comparable in somatostatin treated and placebo group. (Table 1) Failed bile duct cannulation occurred in 11 cases (6.9%) due to technical difficulty. 66 patients (41.2%) had a normal ERCP. 61 patients (38.1%) had stone disease and 15 patients (9.4%) had biliary stricture. The remaining 7 patients (4.4%) had dilated bile ducts of unknown significance. (Fig. 1) Therapeutic procedure was required in 65 patients (40.6%). These included 56 papillotomies (35%), 36 stone extractions (22.5%), 31 insertion of plastic stents (19.4%), and 12 cytology brushings (7.5%). (Fig. 2) No pre-cut papillotomy was performed in the patients studied.

Patients with pancreatitis:

Overall, 10 patients (6.3%) developed post ERCP pancreatitis. 8 cases were mild and 2 cases were moderate. All pancreatitis were self-limiting and uncomplicated. For cases with mild pancreatitis, hospitalization was prolonged for 2 days in 3 patients and 3 days in 5 patients. None of them required analgesics for relief of abdominal pain. For cases with moderate pancreatitis, one patient had CBD stones with papillotomy and stone extraction performed. He required prolonged hospitalization for 7 days and 2 doses of analgesic for relief of abdominal pain during his stay. The remaining patient had a normal ERCP. CT scan abdomen on day 3 pancreatitis revealed only oedema of pancreas without necrosis or abscess formation. Hospitalization was prolonged for 8 days and 2 doses of analgesic were given for pain relief.

Concerning the underlying diagnosis, 5 patients had common bile ductal stones. Of those 5 patients, 4 patients had therapeutic procedures performed and one of them developed moderate pancreatitis. Bile duct access and drainage was failed in the remaining patient which was subsequently successful in the repeated ERCP session. 3 patients had normal ERCP. One of them developed moderate pancreatitis. The remaining 2 patients had malignant bile duct stricture with drainage procedures performed.

There were 4 patients (5%) in the somatostatin group and 6 patients (7.5%) in the placebo

group with pancreatitis. The difference was not statistically significant (P-value = 0.75). (Table 2) Each group has 1 patient with moderate pancreatitis (P-value =1.0).

Patients with hyperamylasemia:

120 patients (75%) developed hyperamylasemia, 61 patients (76%) in the somatostatin group and 59 patients (74%) in the placebo group. The difference was not statistically significant (P-value = 0.72). When only hyperamylasemia of >3 times the upper limit of normal was considered, 31 and 26 patients in somatostatin and placebo group respectively developed significant hyperamylasemia. There was no statistical significant difference between the two groups (P-value =0.41). (Table 2)

The amylase levels at 4-hour post ERCP were 488 (+/- 653) IU/L and 463 (+/- 642) IU/L in the somatostatin and placebo group respectively (P-value =0.51). The amylase levels at 18-hour post ERCP were 462 (+/- 765) IU/L and 409 (+/-619) IU/L in the somatostatin and placebo group respectively. (P-value =0.53). No statistical significant difference was present between the two groups at 4-hour or 18-hour amylase level. (Table 2)

Patients with persistent abdominal pain:

16 patients (10%) developed persistent post ERCP abdominal pain. Equal number of patients occurred in either group (P-value =1.0). (Table 2)

Risk factors for post ERCP pancreatitis:

Patient related and procedure related factors were compared between the two groups of patients with or without pancreatitis. (Table 3) There was no statistical significant difference between the two groups in terms of age, sex, indications for ERCP, proportion of patients with raised bilirubin level, endoscopic diagnoses, proportion of patients requiring therapeutic ERCP, the different types of endoscopic procedures performed, and the number of pancreatic duct injections.

Acute pancreatitis was an indication for ERCP in 5 patients. All of them were suspected to have biliary pancreatitis. Of those 5 patients, 4 patients had stone disease as underlying diagnosis with therapeutic procedures performed. The remaining patient had a normal ERCP. None of them developed post ERCP pancreatitis.

Longer procedure time (P-value=0.002), difficult selective biliary cannulation (P-value=0.016), increased number of pancreatic duct cannulation (P-value=0.024), secondary or higher degree of opacification of pancreatic duct (P-value=0.035) were identified as risk factors for post ERCP pancreatitis on univariate analysis. (Table 3)

After multivariate analysis, only longer procedure time was found to be an independent risk factor for post ERCP pancreatitis (P-value=0.019). Secondary or higher degree of opacification of pancreatic duct had near statistical significance (P-value=0.055). (Table 4)

Side effects of medication:

No adverse side effects of medication (somatostatin or placebo) were reported.

Discussion

Incidence of pancreatitis

Our study revealed an incidence of pancreatitis of 7.5% in the placebo group. This is comparable to the incidence described in a recent prospective study from R Poon et al. in Hong Kong (11). They revealed an incidence of pancreatitis of 10% in the placebo group during a study on the effect of somatostatin infusion for preventing post ERCP pancreatitis. Another recent retrospective clinical audit on ERCP collected data from 13 different hospitals in Hong Kong from January to March in 1999 (12). The incidence of pancreatitis was 1.4% in the 732 ERCPs studied.

Prospective studies from overseas reported an incidence ranging from 2.8% to 10.2% (7-10) for unselected cases, and 12.5% to up to 31% for high risk patients performing invasive procedures (8,24,25). The variation in incidence could be due to a number of reasons: 1) the difference in the definition of pancreatitis, 2) the selection of patients with high risk indication or high risk procedures in some studies, and 3) the difference in case mix and therapeutic procedures performed in individual studies on unselected patients. Thus, the case mix in tertiary centres is more likely to encounter high risk patients with sphincter of Oddi dysfunction performing manometry or pancreatic sphincterotomy, and difficult cases with previously failed ERCP referred from peripheral centres.

Effect of bolus somatostatin

In our study, the difference in the incidence of pancreatitis in the somatostatin group (5%) and the placebo group (7.5%) did not reach statistical significance.

J.M. Bordas et al. (4) in 1988 prospectively studied 49 patients undergoing ERCP. By comparing a prophylactic bolus injection of somatostatin at 4mcg/kg to placebo, he was able to demonstrate a significant reduction in amylase level and only a trend towards decreased incidence of pancreatitis. It was not surprising that the difference in incidence of pancreatitis could not be demonstrated with the small sample size in the study. A subsequent prospective, randomized, placebo controlled study by J.M. Bordas et al. (20) in 1998 included 160 patients. He finally demonstrated a significant reduction in both amylase level and the incidence of pancreatitis. The incidence of pancreatitis was reduced from 10% in the placebo group to 2.5% in the somatostatin group. By breaking down into subgroups, the incidence of pancreatitis was

significantly reduced in the sphincterotomy group but not in the diagnostic ERCP group. Although our study shared a similar definition of pancreatitis and sample size with the study from J.M.Bordas (20), there exists other differences that may explain the discrepancy in our results.

Firstly, we included all patients with or without pancreatic duct manipulation and injection. Whereas in the study by J.M. Bordas, only patients with pancreatic duct contrast filling were included. It probably implies more pancreatic irritation in their patient population when compared to ours. This is reflected in the lower incidence of pancreatitis in our placebo group. (7.5% Vs 10%) The second difference is related to the procedure time. The study by J.M. Bordas had a mean procedure time of 24 $\pm$ 12 minutes whereas our study had a longer mean procedure time of 41 $\pm$ 38 minutes. We speculate that although a bolus dose of 250mcg somatostatin is potent enough to inhibit pancreatic secretion, its effect may not last long enough for the whole ERCP procedure in our patients such that pancreatic injury in the later part of ERCP was not protected by somatostatin. This is reflected in the higher incidence of pancreatitis in our somatostatin group when compared to the somatostatin group from J.M. Bordas (5% Vs 2.5%). Thus, the combination of both factors (a lower incidence of pancreatitis in our placebo group and a higher incidence of pancreatitis in our somatostatin group) results in a smaller difference in effect with somatostatin such that the efficacy of somatostatin could not be demonstrated with the sample size in our study.

Risk factors for post ERCP pancreatitis

The identification of predisposing factors for post ERCP pancreatitis is important in risk stratification in order to allow optimal decision for alternative investigation or therapy. It would also be more effective in preventing pancreatitis by targeting prophylactic therapy to particular high risk groups.

The potential role of a number of patient related and procedure related factors have been proposed and evaluated in different studies. However, it was often difficult to identify independent risk factors in multivariate analysis because of the relatively small sample size and thus infrequent patient events (26).

S. Loperfido et al. (13) studied the major complications of diagnostic or therapeutic ERCP in 2769 patients. ERCP was defined as therapeutic when sphincterotomy, pre-cut, or drainage procedures had been preformed. In 1827 patients undergoing therapeutic ERCP, age less than 70, pancreatic duct opacification, non-dilated common bile duct were identified as independent

risk factors in multivariate analysis. M.L. Freeman et al. studied the complications of biliary sphincterotomy in 2347 patients, pancreatitis was noted in 5.4% of cases. Five significant risk factors were identified for pancreatitis in multivariate analysis: two were patient related factors (suspected sphincter of Oddi dysfunction, younger age), and three were related to difficulty in gaining biliary access (difficult cannulation, higher number of pancreatic duct injections, and pre-cut). M.L Freeman et al. also performed a recent prospective, multicentred study conducted at 11 centres in the United States to evaluate the risk factors for post ERCP pancreratitis (10). Of 1963 ERCPs, pancreatitis occurred in 6.7%. Nine multivariate risk factors were identified: five were patient related (prior post ERCP pancreatitis, suspected sphincter of Oddi dysfunction, female gender, normal serum bilirubin, and absence of chronic pancreatitis) and four were procedure related (biliary sphincter balloon dilation, difficult cannulation, pancreatic sphincterotomy, and opacification of pancreatic duct). Small bile duct diameter, sphincter of Oddi manometry, biliary sphincterotomy, and endoscopist performing <= 2 ERCP/week were significant risk factors only in univariate but not multivariate analysis.

In our study, longer procedure time, difficult selective biliary cannulation, increased number of pancreatic duct cannulation, secondary or higher degree of opacification of pancreatic duct were identified as risk factors for post ERCP pancreatitis in univariate analysis. However, only longer procedure time could be identified as an independent risk factor for post ERCP pancreatitis on multivariate analysis. The inability for other relevant factors in univariate analysis to become significant in multivariate model probably was due to insufficient sample size and patient events. Therapeutic ERCP (including papillotomy, stenting, stone extraction, cytology brushings) did not increase the risk of post ERCP pancreatitis. Performing ERCP on patients with acute biliary pancreatitis after the acute stage appeared to be safe as none of the 4 patients in the study developed post ERCP pancreatitis.

Pathophysiology of post ERCP pancreatitis

Although the detailed pathophysiology and sequence of events in pancreatitis is not yet well delineated, it is generally accepted that, whatever the initiating event, there is an early pancreatic acinar injury with premature enzyme activation and autodigestion (27). This is followed by chemokine production locally at the site of injury (27,28). The attracted polymorphs and macrophages produced a variety of cytokines, triggering a cascade of systemic inflammatory response of varying severity (27).

With the time of onset of pancreatitis specified, ERCP provides a unique model for clinical study of prophylactic drug treatment for pancreatitis and allows the initial cytokine and acute

phase response of pancreatitis to be examined (29). Mechanical injury (from repeated cannulation, therapeutic manipulations around the papilla, and stenting), thermal injury (from papillotomy), chemical injury (from radioapaque contrast), hydrostatic injury (from contrast injection, sphincter of Oddi manometry) may play a role as an initiating event in the pathogenesis of post ERCP pancreatitis (23).

Somatostatin

Since its incidental discovery during a search for growth hormone releasing hormone in 1986 and subsequent rediscovery and isolation in 1972, somatostatin is found in virtually every organ in the body, mainly the central nervous system and the gastrointestinal tract (30,31). It occurs as a decatetrapeptide S14 with a cyclic conformation linked by disulphide bonds, or S28 (an amino terminal extended somatostatin), or prohormone (preprosomatostatin). The same unique S14 peptide has its well-conserved structure in different animal species, in protochordate plants, in protozoa and even prokaryotes, signifying its selective advantage and importance in evolution (30).

At different parts of the body, it serves through its inhibitory action, as a neurotransmitter, an endocrine hormone, a paracrine hormone, an autocrine hormone, or a “lumone”(modify acid and gastrin secretion through intraluminal secretion) (30-33). It is metabolised rapidly locally by capillary aminopeptidases in the brain and by aminopeptidases and endopeptidases in the gastrointestinal tract, explaining its short half-life of ½ min. to 3 minutes (30).

The rationale in using somatostatin for pancreatitis stems from its potent, dose dependent inhibitory effect on concentration and volume of pancreatic enzyme secretion, and bicarbonate output. A dose of 0.15mcg/kg/hr or more has been shown to inhibit pancreatic exocrine secretion effectively (21). It acts through its inhibition on CCK, nervous transmission, and secretin (21,33). By reducing pancreatic output, somatostatin has been reported to be useful in treating persistent pancreatic or gastrointestinal fistula (34,35). There were also case reports of successful treatment of pancreatic pseudocysts with somatostatin (36) and its synthetic analogue (37), and pancreatic ascites (38). Its analogue, octreotide, can also reduce complications after pancreatic surgery (39,40).

Apart from its effect on pancreatic secretion, somatostatin analogue has been shown to be potent stimulators of hepatic reticuloendothelial system in animal studies (41,42). In experimentally induced pancreatitis, the activity of the reticuloendothelial system was found to be impaired (42). With the fact that endotoxemia is associated with more severe pancreatitis,

(43) octreotide may improve the severity of pancreatitis through stimulation of the reticuloendothelial system, thereby reducing endotoxemia. Besides, by inhibiting the formation and release of platelet activating factor, which is thought to be responsible for the pulmonary complications, somatostatin improves lung function in acute pancreatitis (44). Furthermore, somatostatin may also be cytoprotective towards the pancreas (45).

Somatostatin in prevention of post ERCP pancreatitis

Despite various possible actions of somatostatin, its efficacy in treatment of acute pancreatitis was inconclusive (46-48). The lack in a strong effect of somatostatin in treating acute pancreatitis may be related to the small sample size in individual studies and a failure to include severe cases with high mortality rate. It could also be related to the intrinsic time delay in giving the drug in the course of pancreatitis. There is usually a time gap between symptom onset of pancreatitis, presentation to the hospital, diagnosis of pancreatitis, and drug treatment such that the cascade of systemic inflammatory response is already set off when treatment is prescribed.

A number of prospective studies have been performed using somatostatin as a prophylactic treatment to reduce the risk of post ERCP pancreatitis (1-5,11,20,49-52). Table 5 is a summary of their results.

While most studies use somatostatin 250mcg/hour (4mcg/kg/hr) infusion for at least 4 hours and up to 26 hours (with or without preceding bolus injection) to prevent post ERCP pancreatitis, 2 studies used a single bolus injection of 250mcg somatostatin (4,20). Only 3 out of 11 studies reported a statistical significant reduction in the incidence of post ERCP pancreatitis (1,11,20). M. Guelrud et al. (1) studied the use of prophylactic somatostain infusion in 16 patients with idiopathic recurrent pancreatitis undergoing balloon dilation of the pancreatic duct sphincter. The incidence of pancreatitis was lowered significantly from 75% in the placebo group to 25% in the somatostatin group. Pancreatitis was also more severe in the placebo group. The study from J.M. Bordas et al. (20) using bolus somatostatin has been discussed. R. Poon et al. (11) performed a double blind, randomized, placebo controlled study on 220 patients undergoing ERCP. Using somatostatin infusion, the incidence of pancreatitis was reduced from 10% to 3%. The other studies either reported 0% incidence of pancreatitis, (2,51,52) showed no difference (3,5,49) or a trend favoring somatostatin but not reaching statistical significance (4,50).

The problem in interpreting many of the previous studies is their relatively small sample size.

The study from J.M. Bordas et al. in 1988 (4) involved 49 patients and that from A. Gorgul et al. in 1996 (50) involved 24 patients. Both studies did show a trend favoring somatostatin in reducing the rate of pancreatitis. The results could have been statistically significant if sufficient number of patients were included in the study. The other problem in interpretation concerns the definition of pancreatitis. Many studies did not give a definition for pancreatitis. 3 studies (G. Tyden et al. in 1986 (2) involving 47 patients, A. Gorgul et al. in 1998 (51) involving 90 patients, and Y. Uzun et al. (52) involving 30 patients) reported 0% of pancreatitis which is unlikely to be purely explained by their sample size. It could be that relatively mild cases of pancreatitis were not considered as complication according to their definition of pancreatitis. The incidence of pancreatitis ranged from 0% to 17% in studies involving unselected patients, again reflecting the likely difference in their definition of pancreatitis.

Because of the relatively small sample size in individual studies, A. Andriulli et al. (53) performed a meta-analysis of 12 prospective controlled trials on somatostatin in the prophylaxis of post ERCP pancreatitis. 10 studies with a total of 646 patients were included for analysis on acute pancreatitis. 10 studies with a total of 643 patients were included for analysis on hyperamylasemia. 6 studies with a total of 380 patients were included for analysis on abdominal pain. Somatostatin was found to be significantly associated with improvement in all three outcomes.

Other possible therapeutic modalities in prevention of post ERCP pancreatitis

Sandostatin (octreotide) is a synthetic analogue of somatostatin which has a half-life of 90 minutes. With its longer half-life, theoretically, it should be superior to somatostatin since it can be given as intravenous or subcutaneous injection. It also provides an opportunity for treatment on an outpatient basis to reduce hospital costs. Clinical studies, however, failed to confirm its effectiveness in preventing post ERCP pancreatitis.

Z. Tulasay et al. (6) prospectively studied 63 patients receiving either subcutaneous octreotide 0.1 mg or placebo before ERCP. There was statistical significant improvement in enzyme changes but no patient in the study developed pancreatitis. To clarify the issue, the author performed another prospective multi-centre trial involving more than 2000 patients (54). Octreotide, which was given as 0.1 mg dose both before and after ERCP, was found to be ineffective in reducing the risk of post ERCP pancreatitis.

P. A. testoni et al. (55) studied 120 patients with high risk for post ERCP pancreatitis. There was no statistical difference in incidence of pancreatitis and 24-hour severe hyperamylasemia

by giving subcutaneous octreotide 0.2 mg tid before ERCP compared with placebo. The trial from J. M. Sternlieb et al. (56) had to be stopped prematurely after recruitment of 84 patients because interim results showed that the octreotide group had a much higher incidence of pancreatitis of 35% compared with 11% in the placebo group. Two other prospective studies, one involved 245 patients undergoing ERCP (57) and the other included 151 patients for ERCP plus spnicterotomy for choledocholithiasis (58). Both failed to show any evidence to suggest that octreotide could protect against post ERCP pancreatitis.

A meta-analysis performed by A. Andriulli et al. (53) included 10 prospective controlled studies on octreotide. With the analysis including 853 patients in 8 studies on acute pancreatitis, 1733 patients in 7 studies on hyperamylasemia, and 1504 patients in 3 studies on abdominal pain, octreotide was found to reduce the risk of post ERCP hyperamylasemia but had no effect on preventing acute pancreatitis or abdominal pain.

The failure of octreotide to demonstrate protection against post ERCP pancreatitis may be related to its constricting effect on the sphincter of Oddi. It increases the basal pressure, frequency and amplitude of contraction of sphincter of Oddi (59,60). This differential effect comparing with somatostatin may be explained by the difference in affinity to different somatostatin receptor subtypes, which belong to the seven-trans-membrane-spanning receptor (SSTR) family. Octreotide has a high binding affinity to SSTR2 and SSTR5, intermediate affinity to SSTR3, but little or no affinity to SSTR1 and SSTR4. Sphincter of Oddi possesses SSTR1 and SSTR4 receptor subtypes to which somatostatin, but not octreoptide, can bind (44). Additionally, octreotide inhibits other GI hormones that relax the sphincter of Oddi. This results in unopposed excitatory input and causes an increase in sphincter contractility (44).

Gabexate mesilate, a protease inhibitor, has its effects on various enzymes including trypsin, kallikrein, plasmin, thrombin, phospholipase A2 and C1 esterase. It has been used to prevent post ERCP pancreatic injury. With a half-life of 55 seconds, it has to be given by intravenous infusion (61). A prospective, randomized, double-blind, placebo controlled study was performed by G. Cavallini et al. (61) on 435 patients undergoing ERCP. By giving intravenous infusion of gabexate mesilate from 30 to 90 minutes before till 12 hours after ERCP, both the level of enzyme elevation and the incidence of post ERCP abdominal pain were significantly reduced. The incidence of pancreatitis was also significantly reduced from 8% to 2%.

The same meta-analysis from A. Andriulli et al. (53) included 6 prospective controlled studies on gabexate mesilate. Analysis was based on 680 patients in 4 studies for acute pancreatitis, 773 patients in 6 studies for hyperamylasemia, and 488 patients in 3 studies for abdominal pain.

All three outcome measures were improved by gabexate mesilate. However, when gabexate mesilate was compared with somatostatin, the latter agent was found to be more effective in terms of the number of patients to be treated to prevent one acute pancreatitis (27 patients Vs 13 patients).

In the search of an effective drug for prevention of post ERCP pancreatitis, **corticosteroid** was noted to be useful in a retrospective study (62). It compared 824 patients receiving corticosteroid before ERCP for a history of iodine sensitivity and 2 control groups, control group 1 including 1000 patients during the same study period, and control group 2 including 1954 patients from the Midwest Pancreaticobiliary Group. The incidence of pancreatitis was 4.6% in corticosteroid group, 7.4% in control group 1, and 9.1% in control group 2. Results were even more significant when only patients with therapeutic ERCP were included. (5.2% in corticosteroid group, 9.7% in control group 1, and 11.2% in control group 2) Unfortunately, the beneficial effect of corticosteroid was not confirmed by two subsequent prospective randomised controlled studies, one involving 160 patients (63), and the other involving 201 patients (64). In one of the two studies, A. Budzynska et al. also studied the effect of **allopurinol** by comparing 100 patients in the treated group to 101 patients in the placebo group (64). Being a xanthine oxidase inhibitor that blocks the generation of oxygen derived free radicals, it may be potentially useful. However, the study failed to demonstrate any effect on the incidence of post ERCP pancreatitis.

Calcium channel blockers have been shown to prevent experimental pancreatitis. Nifedipine was studied recently by a French group (65) on 155 patients in a prospective randomised controlled trial. Again, no beneficial effect was found.

Interleukin 10 is a major anti-inflammatory cytokine, inhibiting the secretion of many proinflammatory cytokines by macrophages, including TNFa. The production and the level of interleukin 10 follows the course of experimentally induced pancreatitis (66). After a bolus intravenous injection, interleukin 10 remains effective for 24 hours (67). In animal studies, intreleukin 10 was able to reduce the severity of pancreatitis and the development of pancreatic necrosis when given before (68,69) or after (69) induction of pancreatitis.

J. Deviere et al. performed a single centred, randomised, double blind, placebo controlled study on interleukin 10 (67). 144 patients undergoing therapeutic ERCP were prospectively studied for the effect of different dose (4mcg/kg and 20mcg/kg) of bolus injection of interleukin 10 in preventing pancreatitis. Therapeutic procedures included 78% biliary sphincterotomy, 18% pancreatic sphincterotomy, 26% bile duct dilation, 2% pancreatic duct dilation, 20% biliary ductal stent, 2% pancreatic ductal stent, and 6% pre-cut papillotomy. Pancreatitis was defined

as a rise in amylase/lipase level >= 3x ULN associated with new or worsened abdominal pain persisting for >4 hours after ERCP. The incidence of pancreatitis was 24% in the placebo group, 10% with the lower dose and 7% with the higher dose of interleukin 10. There was a statistical significant reduction in the incidence of pancreatitis with interleukin 10 while having little effect on pancreatic enzymes.

Besides medical therapy, main pancreatic duct stenting has also been evaluated in high risk patients to prevent post ERCP pancreatitis. P. R. Tarnasky et al. (70) studied 80 patients with sphincter of Oddi dysfunction undergoing biliary sphincterotomy and S. Sherman et al. (71) studied 93 patients requiring pre-cut sphincterotomy. With prophylactic pancreatic duct stenting, both studies demonstrated a reduction in the incidence of pancreatitis. However a study from A. Smithline et al. (72) on patients performing ERCP with sphincter of Oddi dysfunction, small common bile duct diameter, or requiring pre-cut sphincterotomy found no difference in the incidence of pancreatitis by stenting the pancreatic duct. Besides, there are problems associated with stenting. It may not be technically successful in the first place. Secondly, it requires another session of ERCP shortly for removal of stent. Thirdly, pancreatitis can occur after stent extraction (70).

Future trends

Somatostatin and gabexate mesilate have been shown to protect against post ERCP pancreatitis. By attacking at a different point in the pathophysiology of pancreatitis, interleukin 10 has shed new light on the prevention of post ERCP pancreatitis. Confirmation on its efficacy awaits further study. At present, it is not cost effective to employ these prophylactic agents routinely on patients undergoing ERCP because their effects are not marked and pancreatitis is usually mild and self-limiting. Future studies should target on combination treatment with these prophylactic agents, which act on different points in the pathophysiology of pancreatitis. The cost effectiveness is likely to improve if therapy is targeted at high risk patients or high risk procedures.

As ERCP is not without risk and that over 40% of our patients had normal ERCP findings, effort should be made to employ more non-invasive investigations like MRCP to look for biliary or pancreatic abnormalities and to exclude normal patients before proceeding to standard ERCP. By comparing MRCP to ERCP findings, J. A. Soto et al. (73) studied 46 patients in the evaluation of biliary tract problems. MRCP was found to have a high sensitivity of 96.3% for bile duct dilatation, 90 % for biliary stricture, 100% for intraductal abnormalities, and a high specificity of 94.1%.

It is hoped that by selecting appropriate patients to undergo ERCP, by refining our instruments and techniques, and by development of more promising prophylactic treatment, risk of pancreatitis could be reduced to its least and ERCP can be performed more safely.

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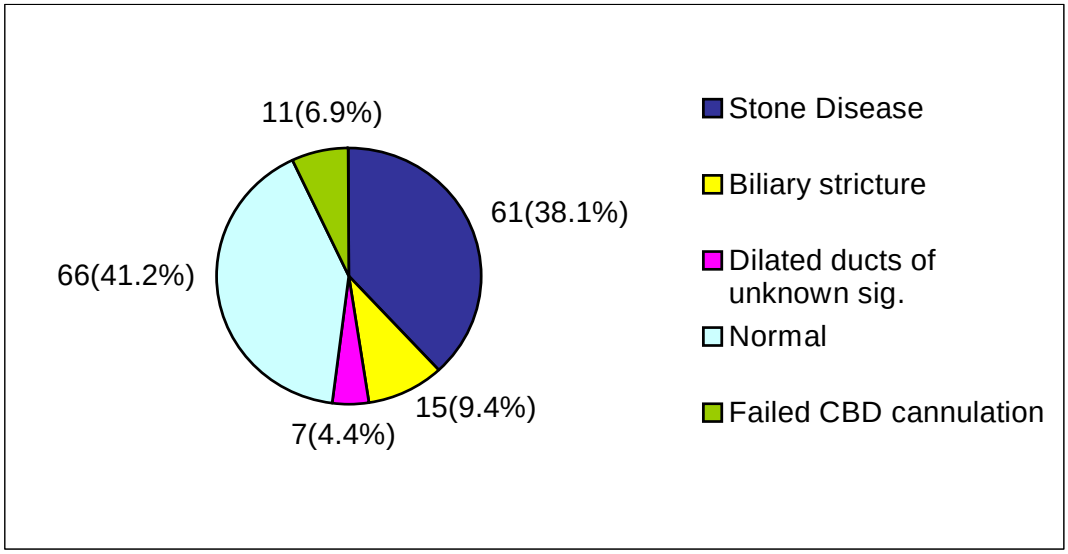

Fig. 1 Endoscopic diagnosis

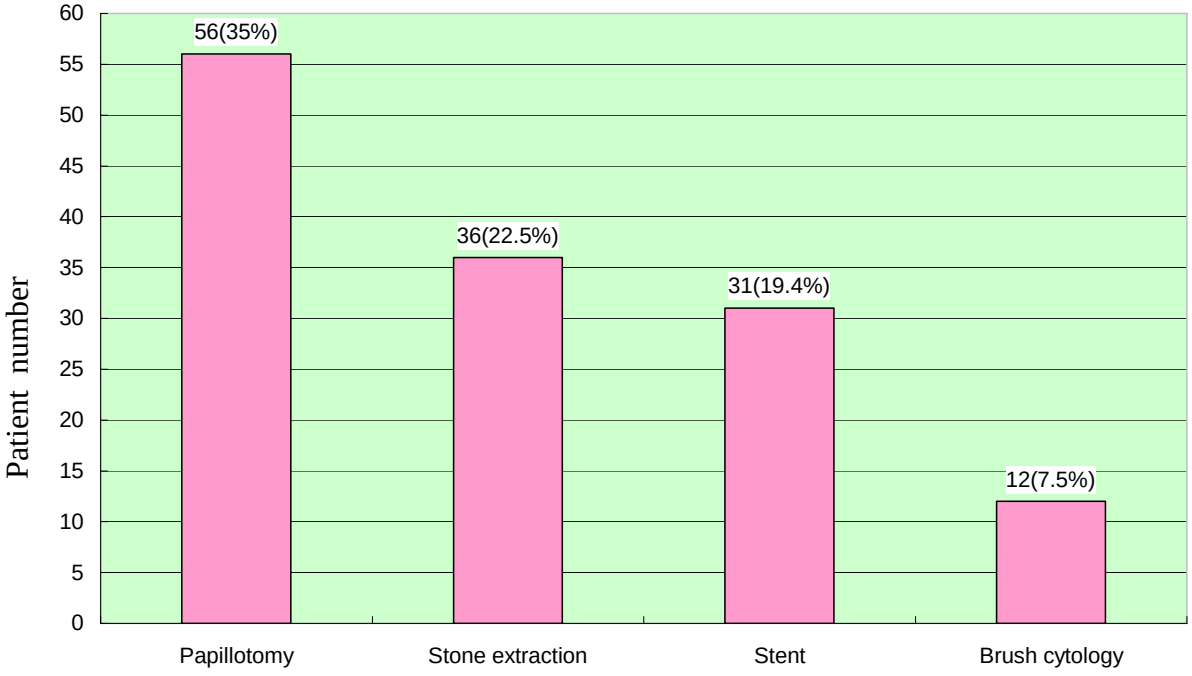

Fig. 2 Endoscopic Procedures

Table 1. Details on patient characteristics, indication for ERCP, endoscopic diagnosis, diagnostic and therapeutic ERCP, and procedure time.

	Somatostatin (n=80)	Placcebo (n=80)	p-value
Sex (M/F)	48/32	42/38	0.34
Age	56±14*	59±13*	0.18
Raised bilirubin	45	35	0.11
Indication			
Cholangitis	8	8	1.0
Acute pancreatitis	3	2	1.0
Abnormal liver function test	41	38	0.64
Suspected stone disease in ultrasound	28	32	0.51
Endoscopic diagnosis			
Stone disease	28	33	0.42
Biliary stricture	10	5	0.18
Dilated bile ducts of unknown significance	5	2	0.44
Normal	31	35	0.52
Failed	6	5	0.76
Procedure	32	33	0.87
Procedure time	41±40*	41±37*	0.89

*mean ± SD

Table 2. Details on pancreatitis, amylase and pancreatic pain.

	Somatostatin (n=80)	Placcebo (n=80)	p-value
Pancreatitis	4	6	0.75
Amylase 0 hour	105±93*	122±131*	0.41**
Amylase 4 hour	488±653*	463±642*	0.51**
Amylase 18 hour	462±765*	409±619*	0.53**
Hyperamylasemia	61	59	0.72
Hyperamylasemia >3x normal	31	26	0.41
Persistent abd. pain 18 hour	8	8	1.0

*mean ± SD

**Student t-test on log amylase

Table 3. Possible risk factors for post ERCP pancreatitis on univariate analysis.

	Pancreatitis (n=10)	No pancreatitis (n=150)	p-value
Patient related factors			
Sex (M/F)	5/5	85/65	0.68
Age	57±14*	58±14*	0.76
Bilirubin (raised/normal)	5/5	75/75	1.0
Indication			
Cholangitis	1(10%)	15(10%)	1.0
Acute pancreatitis	0	5(3%)	1.0
Abnormal liver function test	5(50%)	74(49%)	0.96
Suspected stone disease on ultrasound	4(40%)	56(37%)	1.0
Endoscopic diagnosis			
Stone disease	5(50%)	56(37%)	0.51
Biliary stricture	2(20%)	13(9%)	0.24
Dilated bile ducts of unknown significance	0	7(5%)	1.0
Normal	3(30%)	63(42%)	0.53
Procedure related factors			
Procedure	6(60%)	59(39%)	0.32
Papillotomy	4(40%)	52(35%)	0.74
Stone extraction	2(20%)	34(23%)	1.0
Stent insertion	4(40%)	27(18%)	0.10
Brush cytology	2(20%)	10(7%)	0.17
Procedure time	79±41*	38±37*	0.002**
Selective biliary cannulation (easy/difficult)	5/5	127/23	0.016**
No. of PD cannulation	5.5±5.0*	2.5±3.3*	0.024**
No. of PD injection	4.0±3.9*	2.1±2.8*	0.1
Secondary or higher degree of PD opacification	7	50	0.035**
Extent of PD opacification			0.101
Nil	1	46	
Head	0	11	
Body	3	34	
Tail	6	59	

*mean ± SD

**statistically significant

Table 4. Risk factors for post ERCP pancreatitis on multivariate analysis

	Pancreatitis	No pancreatitis	p-value
Procedure time	79±41*	38±37*	0.019**
Opacification at2nd degree or more	7	50	0.055

*mean ± SD

**statstically significant

Table 5. Summary of 11 prospective studies on somatostatin for prevention of post ERCP pancreatitis. (1-5,11,20,49-52)

	Author	Pt. no.	Study design*	Definition of pancreatitis	Somatostatin treatment regime	Incidence of pancreatitis	Incidence of hyperamylasemia	Effect on pancreatitis	Effect on amylase level
1.	G. Tyden et al. 1986 (2)	47	P, HC	N/A	250 mcg/hr infusion for 24 hrs	0%	58%	NS	NS
2.	A. Saari et al. 1988 (3)	56	P, PC	N/A	250 mcg bolus injection followed by 250 mcg/hr infusion for 3 hrs	10%	55%	NS	NS
3.	P.A. Testoni et al. 1988 (49)	54	P, PC	N/A	250 mcg/hr infusion for 26 hrs	18.5%	N/A	N/A	NS (30% ↓ in unselected patients 40% ↓ in patient with recurrent pancreatitis
4.	J.M. Bordas et al. 1988 (4)	49	P, PC	Simultaneous abd. pain, rise in lipase and amylase level	A single injection 4 mcg/kg	12%	94% (placebo gp.) 50% (treatment gp.)	NS (a trend towards decreased incidence of pancreatitis)	Significant reduction
5.	M. Guelrud et al. 1990 (1)	16	P, PC	Abd. Pain + amylase and lipase > 3x ULM	250 mcg/hr 1 hr before balloon dilation for 12 hrs	75% (in placebo group)	N/A	Significant reduction (75% in placebo gp., 25% in somatostatin gp.	
6.	B. Persson et al. 1992 (5)	54	P, PC	rise in amylase or lipase and/or signs of pancreatitis	300 mcg/hr for 3½ hrs, then 140 mcg/hr for 1 hr	17%	90%	NS	NS
7.	A. Gorgul et al. 1996 (50)	24	P, PC #	N/A	3.5 mcg/kg bolus injection followed by 250 mcg/hr infusion for 4 hrs	25%	N/A	NS (1 in treatment gp., 5 in placebo gp. developed pancreatitis)	N/A
8.	J.M. Bordas et al. 1998 (20)	160	P, PC	Amylase >600iu/m and lipase >200iu and abd. pain for >18hrs	A single injection 4 mcg/kg	10%	N/A	Significant reduction in sphincterotomy gp., not significant in ERCP diagnostic gp.	NS
9.	A. Gorgul et al. 1998 (51)	90	P, PC	N/A	3.5 mcg/kg bolus injection followed by 250 mcg/hr for 4hrs	0%	N/A	NS	Significant reduction
10.	Y. Uzun et al. 1999 (52)	30	P, PC	N/A	250 mcg/hr infusion for 6 hrs	0%	N/A	NS	NS
11.	R. Poon et al 1999 (11)	220	P, PC	Amylase or lipase >3x ULN and abd. pain for 24 hours	250mcg/hr for 12½ hrs	10% (in placebo gp.)	53%	Significant reduction (10% in placebo gp., 3% in somatostatin gp.)	NS (lower amylase level in somatostatin gp.)

- Study design: P= Prospective, PC= Placebo control, HC= Historical control

#= study on patients performing sphincterotomy or sphincter of Oddi manometry