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Review

Prevention of post ERCP pancreatitis: An overview

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SUMMARY

Therapeutic ERCP has become an accepted interventional method for both biliary and pancreatic diseases despite complications. Post-ERCP pancreatitis, a complication associated to the technique and the endoscopist's skills, remains a burning issue since it has been reported to occur in 2-9% in unselected prospective series, and up to 30% in some series due to diverse definitions of post-ERCP pancreatitis and different methods of data collection. The severity of post-ERCP pancreatitis can range from a minor inconvenience, to a devastating illness (0.3% to 0.6% in prospective series) with pancreatic necrosis, multiorgan failure, permanent disability, and even death. Patient-related risk factors (i.e. patient indication selection, young age, sphincter of Oddi dysfunction, female sex, previous pancreatitis, potentially pancreatotoxic drugs, anatomic variations) and endoscopy-related factors (precut sphincterotomy, injection of contrast media into the pancreatic duct, difficulty of cannulation), have all been reported to increase the risk of developing post-ERCP pancreatitis. Pharmacological agents, such as nifedipine, glucagon, calcitonin, n-acetylcysteine, allopurinol, corticosteroids, low-molecular weight heparin, gabexate, somatostatin and its analogues, have been proposed with the indication of avoiding post-ERCP pancreatitis. Novelties in cannulation techniques and improved equipment, along with specific endoscopic interventions, as prophylactic pancreatic stent placement, have also been proposed to effectively reduce the risk. This review provides an evidence- based assessment of published data on prevention of post-ERCP pancreatitis and current suggestions for its avoidance.

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INTRODUCTION

Although therapeutic ERCP has become an established interventional method for biliary and pancreatic disease (biliary drainage due to malignancies, pancreatic pesudocyst drainage, biliary duct stones, etc), the major drawback of acute pancreatitis is always the most feared complication of ERCP. Prospective series of non-selected patients reported a frequency of post-ERCP pancreatitis (PEP) that ranged between 2.1 and 39%. This varying incidence has been considered a result of multiple factors such as thoroughness of follow-up, definition used, and parameters relating to patient susceptibility, case mix, types of manoeuvres performed, and the endoscopist. Recently, two large studies reported incidence of PEP at 15.1% and 12.1% respectively. The first one was a prospective multicenter study where the elevated PEP incidence was attributed to a high percentage (33.9%) of suspicion of Oddi dysfunction as indication for the procedure.[1] The second was a retrospective study reporting risk factors in a population of patients that had undergone pancreatic sphincterotomy, which is "per se" a well-known risk factor.[2] Nonetheless, the largest prospective studies typically report an incidence of post-ERCP pancreatitis ranging from 1-9 % in unselected patients.[3-9] Although most episodes of PEP are mild (about 90%), a small percentage of patients (about 10%)[10-12] may develop severe pancreatitis; these patients have significant morbidity and mortality since systemic inflammatory response, pseudocyst development and multisystem organ failure may occur.

The definition of post-procedure pancreatitis still remains a controversial issue in the field of post-ERCP/ sphincterotomy complications, due to the different parameters and criteria adopted. Duration of pancreatic-type pain and the amplitude and duration of serum amylase increase are both crucial points in the definition and grading of the pancreatic reaction. Controversy also exists regarding pancreatitis severity; thus definition criteria have

been proposed. The Atlanta classification for pancreatitis severity, classifies this complication as mild or severe on the basis of the absence or presence of local (documented by CT) scan) or systemic complications, independently of the duration of the hospital stay.[13] It has been proposed that epigastric pain persisting for at least 24-48 hours,[14] or requiring a hospital stay of more than 48 hours, along with elevation of serum amylase level greater than 3 times or more the upper normal limit should be considered a predictor of ongoing pancreatitis.[15]

Regardless of the mechanism that initiates post-ERCP pancreatitis, once activated, the pathways of inflammation are similar to those for other forms of pancreatitis.[16-18] Numerous mechanisms, mechanical, chemical, enzymatic and infectious have been postulated for the induction of post-ERCP pancreatitis. Mechanical reasons include elevation of intrapancreatic duct pressure due to obstruction of the pancreatic juice flow. Cannulation trauma to the papilla is the most common cause of sphincter of Oddi spasm[19] and/or an edema of the papilla, thus creating an obstacle to the flow of pancreatic juice,[20] and subsequently injection pressure contributes to ductal epithelial or acinar injury. Several studies have demonstrated a correlation between the elevation of serum pancreatic enzyme levels, the volume of the contrast medium injected[21] and the degree of duct opacification.[22-24] On the basis of the concept that pancreatic outflow obstruction is a major risk factor for post-ERCP pancreatitis, temporary placement of a pancreatic stent has been shown to be beneficial,[25-31] particularly in high-risk candidates.[32]

During the last 2 decades, many studies have addressed the issue of possible risk factors for PEP and thus, by identifying them, to prevent this complication. Multivariate analyses have delineated patient- and procedure-related factors associated with the risk of this complication, so that post-ERCP pancreatitis is now largely predictable.[3, 4, 7-8, 33-35] ERCP should not be proposed when other less invasive or non-invasive techniques can achieve imaging of the pancreaticobiliary tree or in patients with a low pre-test probability of benefiting from the procedure. Regarding patient related risk factors studies have implicated female gender, young age, suspected Oddi sphincter dysfunction (SOD), history of prior PEP, recurrent acute pancreatitis and normal bilirubin levels being the most common. Papillary trauma, difficult cannulation, precut sphincterotomy, biliary and pancreatic sphincterotomy, injection of contrast media into the pancreatic duct, balloon-dilation of the biliary sphincter have all been reported to lead to an increased risk of developing post-ERCP pancreatitis.

This review provides a comprehensive, evidence-based assessment of published data on prevention for post-ERCP pancreatitis. We searched the MEDLINE database (January 2007- January 1990) by using the following medical subject headings (MESH): post ERCP pancreatitis, pancreatitis, ERCP, ERCP complications, post ERCP pancreatitis. The references lists cited in all articles retrieved from Medline were searched for additional studies not found in the computerized database search.

Pharmacologic prevention

Pharmacotherapy has been widely studied in the prevention of PEP during the last three decades. Up to now, routine prophylaxis has not been adopted in the majority of centers that conduct ERCP procedures or recommended in guidelines. This means that most endoscopists in the ERCP field believe that expertise and technique, more than pharmacologic prophylaxis, play a major role in the prevention of postprocedure pancreatitis. Medications to prevent PEP can probably be classified into those that affect sphincter pressure or contractility and those that affect pancreatic secretion. Topical lidocaine spray on the papilla, IV nifedipine, glyceryl trinitrate, subcutaneous low molecular weight heparin, prednisone, allopurinol, N-acetylcysteine, IV recombinant human IL-10, diclofenac, somatostatin, octreotide, and gabexate have all been evaluated. In these studies, a given drug has been tested with different dosages or modalities of administration with contradictory results, or results from small studies have not been confirmed (Table 1).

Agents affecting sphincter function

Several agents have been used in an effort to relax the sphincter of Oddi and to promote pancreatic drainage and, thereby, prevent pancreatitis. Nifedipine, a calcium channel antagonist, decreases the basal pressure at the sphincter of Oddi. It also lowers the amplitude, shortens the duration and decreases the frequency of sphincter contraction in healthy volunteers.[36] This agent was ineffective in two trials that randomized 321 patients to receive regular or long acting nifedipine or placebo.[37,38]

The results with nitroglycerine in two randomized trials were more encouraging. Nitroglycerine (glyceryl trinitrate) administered sublingually or transdermally, reduces sphincter of Oddi basal pressure and motility in normal individuals and relaxes the sphincter.[39] In one study, 186 patients at average risk for pancreatitis were randomized to sublingual nitroglycerine or placebo before ERCP, and a significant reduction in the frequency of pancreatitis was observed in the nitroglycerine group (7.7% vs. 17.8%; $p < 0.05$); the drug was primarily effective in patients undergoing diagnostic ERCP and in those who had cholangi-

Table 1. Proposed medications for PEP prevention

Drug	Suggested way of action	Effective in prospective RCT
Calcium channel blockers	Sphincter spasm	No
Nitroglycerine		Conflicting data
Topical lidocaine spray		No
Antibiotics	Infection	Conflicting data, need for more trials
Ocreotide	Pancreatic secretion	Conflicting data
Somatostatin		Conflicting data
Corticosteroids	Inflammation cascade	No
Allopurinol		Conflicting data
N-acetylcysteine		No
Platelet activating factor Inhibitors		No
Interleucin-10		Conflicting data
Heparin		Conflicting data
Gabexate		Conflicting data
Diclofenac (NSAIDs)		Yes in only one study, need for more trials

ography alone, which generally is low risk.[40] In the other study, 144 patients at average risk were randomized to a nitroglycerine patch or a placebo.[41,42] There was a significant reduction in the frequency of pancreatitis in the nitroglycerine group (4% vs. 15%; p=0.03) and by multivariate analysis treatment with nitroglycerine was independently significant. The scepticism in both of these studies includes unusually high rates of pancreatitis in the control groups (low- to average-risk patient groups) and limited assessment of efficacy in higher-risk patients. Kaffes et al evaluated the effect of transdermal GTN in facilitating cannulation or PEP prevention in either average or high-risk patient groups.[43] No difference in cannulation times or difficulty was appreciated and there was no difference in the incidence of post-ERCP pancreatitis. This study also had the reservation of small statistical sample. Furthermore, it is not surprising that nitroglycerin had no apparent effect on facilitating cannulation. Mechanical factors such as the angle between the ducts and ampulla and papillary stiffness are probably more important determinants of successful cannulation than the size and patency of the papillary orifice.[44]

A topical spray of lidocaine on the papilla has been proposed to have a relaxing effect based on the fact that this agent blocks intramural neural reflexes in the small intestine and the sphincter of Oddi. However, a randomized trial in average-risk patients with a low background rate of pancreatitis did not demonstrate efficacy.[38]

Prophylactic antibiotics

Administration of antibiotics was postulated by one group of investigators to prevent pancreatitis by limiting secondary infection. A randomized trial in 321 patients compared prophylactically administered ceftazidime to placebo: the frequency of pancreatitis was significantly lower in the antibiotic-treated group (2.6% vs. 9.4%; p=0.009), a finding sustained in a multivariate analysis with a limited number of potentially confounding variables.[45] In another randomized controlled trial of 100 patients no significant difference was found in the incidence of PEP between the group treated with intravenous cefotaxime and the group given placebo (4% versus 6%).[46] These conflicting data need to be verified in larger studies.

Agents interfering with the inflammatory cascade

Efforts to prevent PEP have focused on a variety of agents that interrupt the inflammatory cascade at various points. Corticosteroid in various forms (methylprednisolone, prednisone, and hydrocortisone) has been extensively investigated as possible means of reducing the incidence of PEP. One retrospective observational study (without adjustment for confounding variables or multivariate analysis) suggested that corticosteroids might be protective.[47] Subsequently, 5 randomized controlled trials, with over 2500 patients, demonstrated no benefit, or any trend toward a benefit, for various corticosteroid formulations.[49-52] Recently, a large multicenter prospective blinded controlled trial[53] enrolled 1115 patients in two groups to receive 40 mgr prednisone per os or placebo, evaluating whether prophylactic corticosteroids) will reduce the incidence of post-ERCP pancreatitis. There was no dif-

ference in the incidence of pancreatitis or the frequency of investigated potential pancreatitis risk factors between the corticosteroid and placebo groups.

In a similar approach, it was hoped that xanthine oxidase inhibitors, such as allopurinol, might prevent PEP by inhibiting generation of oxygen-derived free radicals. Allopurinol has been evaluated in two randomized controlled trials of approximately 1000 patients in total. Both trials found no difference in the frequency of PEP in patients given allopurinol compared with those given a placebo.[48,54] According to Katsinelos et al, pre-treatment with high-dose, orally administered allopurinol decreases the frequency of PEP.[55] Of special interest is the fact that total rates of pancreatitis of all 3 studies in the allopurinol groups (62 of 579, 10.7%) and the placebo groups (71 of 565, 12.6%) are not statistically different.[56] Of note, the allopurinol dosage and the timing of administration differ among all 3 studies: 600 mg at 15 and 3 hours before ERCP in the Katsinelos study, 600 mg at 4 hours and 300 mg 1 hour before ERCP in the Mosler study, and 200 mg at 15 hours and 3 hours before ERCP in the Budzynska study. The negative findings in the Mosler study argue strongly against the theory that insufficient quantities of allopurinol explained the disparity in findings in the Katsinelos and Budzynska studies. In a similar context, another free radical scavenger, N-acetylcysteine, was studied as a possible agent for PEP prevention. A prospective, double-blind, placebo-controlled trial was conducted in 256 patients randomized to receive intravenous N-acetylcysteine at a loading dose of 70 mg/kg 2 hours before and 35 mg/kg at 4-hour intervals for a total of 24 hours after the procedure, or to receive normal saline solution as placebo.[57] There were no statistical differences in the incidence of PEP, severity grades or the mean duration of hospitalization for pancreatitis between the groups.

There are studies of inhibitors of the platelet-activating factor for the experimental and clinical modulation of the severity of acute pancreatitis. Unfortunately, the preliminary results of a large, multicenter, prospective, randomized trial do not indicate any reduction in PEP when using these agents.[58] Recombinant interleukin 10 (IL-10) has been evaluated for prophylactic immunomodulation of the pro-inflammatory cascade, with encouraging results in experimental models.[59,60] A randomized trial that included 144 higher-risk patients undergoing ERCP found lower rates of pancreatitis in each of two treatment groups (3% and 5%) vs. the control group (11%) ($p < 0.05$). Multivariate analysis showed the distribution of risk factors was somewhat imbalanced between the groups; however it disclosed IL-10 association with a decreased likely hood of developing PEP [OR 0.46, 95% CI 0.22-0.96; p=0.39].[61] In contrast, another study of average-risk patients in which a lower dose of IL-10 (8 mcg/kg) was administered failed to demonstrate any significant difference, or any trend toward a difference, in the frequency of pancreatitis in treated patients (11%) vs. those given a placebo (9%).[61] A meta-analysis of published data suggested that IL-10 was effective in preventing PEP with a frequency of 7.1% in the treated group vs. 13.9% in the placebo group (p=0.003), thus, raising a hope that this drug is effective.[62]

The newest but simplest agent for interrupting the inflammatory cascade, based partly on its ability to inhibit phospholipase A2, is diclofenac, an orally administered non-steroidal anti-inflammatory drug (NSAID). A single randomized trial in 220 patients suggested that diclofenac given as a rectal suppository immediately after ERCP, was associated with a 6.4% frequency of pancreatitis compared with 15.5% in a control group (p=0.049).[63] NSAIDs can inhibit the early inflammatory cascade involving phospholipase-A2, prostaglandins, or endothelial neutrophil attachment during acute pancreatitis. A larger multicenter study is needed to confirm the protective role of NSAIDs since this was a single center study and diclofenac was not effective in the subgroup of patients with SOD, the very group of patients that are at greatest risk. There is also the further concern for the potential adverse effects of NSAIDs with respect to renal function and bleeding.

One of the most promising agents for prevention of PEP, used in routine clinical practice in some parts of the world, especially in Asia, is the protease inhibitor gabexate.[5,64] Prevention of intra-acinar trypsinogen activation to trypsin and the subsequent inflammatory cascade may be achieved by using antiprotease agents. In 1995, a study[65] on the first attempt at using C1-inhibitor (C1-INH) plasma concentrate was published. The blockage of ongoing complement and contact system activation by high doses of C1-INH has been reported to improve the outcome of acute pancreatitis in experimental models.[66] Gabexate mesilate was shown to be effective in preventing post-ERCP pancreatitis in a prospective, multicenter, controlled trial involving 418 patients: the incidence of pancreatitis was reduced four-fold in the treatment group compared with the placebo group (2% vs. 8%).[5,67] An initial meta-analysis of these two trials suggested that gabexate significantly reduced the risk of pancreatitis (OR 0.27: 95% CI [0.13, 0.57]); the number needed to treat to prevent one episode of pancreatitis was relatively high at 27.[67] A subsequent large multicenter study of gabexate as a single dose before ERCP and continued for 2 hours thereafter found no significant difference in the frequency of pancre-

atitis in the treatment group (8.1%) vs. the placebo group (6.5%). A second meta-analysis from the same group including papers published up to 2003 on the prevention of post-ERCP pancreatitis with somatostatin and gabexate, in both standard and high-risk patients, suggested that when all studies were combined, gabexate was barely effective (OR 0.58: 95% CI [0.34, 0.99]), with the number needed to treat being 35; in addition, gabexate given as a short-term infusion (<4 hours) was found to be ineffective.[35] A disadvantage of the gabexate mesilate prophylaxis is the need for a 12-hour infusion; however, a recent multicenter study by the same group has demonstrated that a 6-hour infusion was as effective as a 12-hour infusion.[64] At the end of last year, Testoni et al reported their experience in over 2400 patients. Data from 1312 patients who underwent ERCP procedures without gabexate prophylaxis and from 1149 consecutive patients with 1g i.v. gabexate, were retrospectively evaluated during a 6-year period. Statistical analysis was also performed in groups of standard- and high-risk subjects and data for cost effectiveness was also assessed. The frequency of pancreatitis appeared significantly reduced in the gabexate period in comparison with the pre-gabexate period in cases overall (2.2% versus 3.9%; p=0.019). However, the reduction was significant only for high-risk patients (3.8% versus 7.3%; p=0.001). Furthermore, gabexate appeared unable to reduce the incidence of severe pancreatitis.[68] A double-blind multicenter prospective randomized controlled trial studied 1127 patients undergoing ERCP to receive intravenous administration of 750 mcg somatostatin, 500 mg gabexate mesylate, or placebo.[69] The drug infusion started 30 minutes before and continued for 6 hours after endoscopy. No significant differences in incidences of pancreatitis, hyperamylasemia, or abdominal pain were observed among the placebo (4.8%, 32.6%, and 5.3%, respectively), somatostatin (6.3%, 26.8%, and 5.1%, respectively), and gabexate mesylate groups (5.8%, 31.5%, and 6.3%, respectively). Recently a third metanalysis including 4 prospective randomized controlled trials, three from Italy and one from China was published.[70] The authors concluded that gabexate mesilate can not prevent pancreatic injury after ERCP. Overall, at present, routine prophylactic administration of gabexate mesilate in all patients undergoing ERCP cannot be suggested.

Heparin has been shown to have anti-inflammatory properties, to inhibit the activity of pancreatic proteases and improve pancreatic circulation. Salas et al[71] found that heparin reduces TNF-alpha-induced inflammation by inhibiting the interaction between leukocytes and endothelium. Rabenstein et al showed in a prospective analysis of risk factors for PEP after ERCP with endoscopic sphincterotomy that the administration of any type of heparin was associated with a reduction in the frequency of AP from 7.9% (43/547) to 3.4% (9/268; p=0.005).[72] There was no increase in the number of bleeding events in the heparin treated group compared with the placebo group. In a study that followed the preliminary report of this observation,[73] heparin significantly improved the course in 3 different experimental animal models (rats) of mild to moderate pancreatitis.[74] Continuous intravenous treatment with unfractionated heparin was started before induction of pancreatitis, and it resulted in significantly reduced edema, inflammation, and peak serum amylase values compared with control animals. However, in a separate randomized controlled study by the same research group in 458 high risk patients, there was no reduction in the incidence of PEP in the low-molecular-heparin group compared to placebo.[75]

Agents affecting pancreatic secretion

The antisecretory agent somatostatin and its long-acting analogue octreotide have been extensively evaluated for the prevention of PEP. Somatostain and octreotide affect the exocrine function of the pancreas directly by reducing the secretion of digestive enzymes and indirectly by inhibiting secretin and cholecystokinin production. Besides their antisecretory effects, somatostatin and octreotide modulate the cytokine cascade and may also have a protective effect on pancreatic cells.[76,77] Furthermore, animal studies have shown that both substances have protective effects in experimental acute pancreatitis. Octreotide has the advantage of simple administration by subcutaneous injection, whereas somatostatin requires continuous parenteral infusion. On the other hand, octreotide stimulates and raises the pressure of the sphincter of Oddi.

Somatostatin has been administered for prophylactic purposes either by 2 to 26-hour prolonged i.v. infusion or by a single bolus administration immediately before the ERCP procedure. Over the last 15 years, over 15 randomized controlled trials and 2 metanalysis have been published. Somatostatin statistically significantly reduced the risk of PEP in only 3[35,78,79] randomized controlled trials. In an initial meta-analysis, of 28 clinical trials with somatostatin (12 papers), octreotide (10 papers), and gabexate (6 papers), somatostatin was found to be effective (OR 0.38: 95% CI[0.22, 0.65]).[67] None of these studies investigated the efficacy in high-risk patients. A subsequent large scale, multicenter, placebo-controlled trial in 382 patients found that a single dose of somatostatin at 750 μg and continued for 2 hours after infusion was in-

effective in preventing pancreatitis; pancreatitis occurred in 11.5% of patients who received somatostatin vs. 6.5% of those given a placebo.[35] A second meta-analysis of somatostatin by the same investigators who performed the first, in which data from short- and long-term infusion studies were pooled, found somatostatin to be ineffective (OR 0.68: 95% CI[0.44 1.04]; p=0.075).[35,80] After publication of the second meta-analysis, another study in 372 patients found that pancreatitis was significantly less frequent (1.7%) in patients treated with a bolus or a 12-hour infusion of somatostatin compared with those given a placebo (9.8%).[81] In summary, somatostatin is possibly efficacious in the prevention of PEP.

Of 10 studies of octreotide, most show no significant reduction in the frequency of PEP compared with placebo.[82,83] Paradoxically, several studies have noted an increase in the frequency of pancreatitis in patients given octreotide, an observation that reached statistical significance in at least one study.[83] This may be explained by the fact that ocreotide also raises the pressure of the sphincter of Oddi, thus contributing to pancreatic outflow obstruction and, hence, pancreatitis.[84] A meta-analysis suggested that octreotide is ineffective in preventing pancreatitis after ERCP.[67] The drawback in this metanalysis data was that none of the studies included investigated the efficacy in high-risk patients. Lung et al[85] in a recent meta-analysis, included 11 randomized, controlled trials accepted as abstracts for Digestive Disease Week for the years 2000, 2001, and 2002, enrolling a total of 2770 patients. No beneficial effect of octreotide in the prevention of post-ERCP pancreatitis was found. Despite these disappointing results coming from 2 metanalysis, Thomopoulos et al, in a study in nonselected cases,[86] published in the November 2006 issue of Gastrointestinal Endoscopy, showed that it is possibly the way of administration and the dosage of the agent that should be changed in order to obtain favorable results, reporting postprocedure pancreatitis rates of 8.9% and 2% in the placebo and octreotide groups ($P < .03$), respectively. These investigators, keeping in mind some important aspects concerning the characteristics of the drug and that the pancreas should be depleted of the intracellular enzyme before the procedure to reduce local damage induced by enzyme activation, started an increased dosage of octreotide administration 24 hours before the ERCP, and not immediately before, as in previous studies; the 24-hour octreotide schedule seems to lower the pancreatic enzyme content.[87,88] To avoid potential effects of octreotide on the sphincter of Oddi motor function, the investigators administered the drug at least 1 hour before the procedure. There was no significant difference between the 2 groups with respect to the difficulty of cannulation, suggesting that giving octreotide at least 1 hour before the procedure does not cause any drug-related increase in cannulation problems. This has also been shown previously.[89] The major concern in this study is the fact that it has not included high risk populations that would benefit the most from chemoprophylaxis. Furthermore, this study presents the same risk as previously considered promising agents, with no larger subsequent study to confirm these data.

TECHNIQUE RELATED PROPHYLAXIS

Pancreatic stents

Trans-sphincter placement of a pancreatic stent is a relatively new and increasingly popular approach to reducing the risk of PEP. Cannulation trauma to the papilla is the most common cause of sphincter of Oddi spasm[19] and/or an edema of the papilla, thus creating an obstacle to the flow of pancreatic juice, and subsequently determines an acute pancreatic inflammation.[20] This mechanism is highlighted by a Japanese group study[90] where the authors showed that, although the frequency of ES-induced pancreatitis is significantly higher than that of post-ERCP pancreatitis, the frequency of severe pancreatitis within 48 hours, and the worsening of pancreatitis after 48 hours is significantly lower within the group of patients who contracted ES-induced pancreatitis. Thus, the lowering of intraductal pressure after ES mitigates the severity of post-procedural pancreatitis. To further support this, Freeman et al have demonstrated that multiple pancreatic duct injections are an independent risk factor in the etiology of acute pancreatitis following ERCP.[3] Another study by Freeman et al confirmed these results, showing that despite pancreatic duct multiple injections and small acinar ducts depiction, the risk for post-ERCP pancreatitis disappeared when endoscopic sphincterotomy was performed.[4] Patients with a patent minor papilla and an accessory pancreatic duct are reported to have a lower incidence of pancreatitis after ERCP despite transient major papilla trauma/edema,[91] perhaps due to pancreatic juice flow via the secondary route, thus protecting the ductal system from overinjection. Theoretically, stents mitigate instrumental papillary trauma and maintain the flow of pancreatic juice, and/or empty the gland of reactive enzyme substrate; therefore, the effects of hydrostatic overpressure to the pancreatic duct are minimized. According to the "plumbing" concept, drainage of manipulated pancreatic ducts should prevent pancreatitis, just as drainage of obstructed bile ducts prevents cholangitis.

Three published prospective randomized controlled trials, seven case control series and one meta-analysis have compared rates of pancreatitis after ERCP with and without

a pancreatic stent.[26-28,30,92-99] These studies have been criticized for inclusion of heterogeneous or high-risk groups of patients (various combinations of pre-cut sphincterotomy, SOD, difficult cannulation, pancreatic sphincterotomy, biliary balloon dilation for stones, papillectomy, and attempted pancreatic stent insertion). All of those studies that enrolled more than 30 patients, found either a trend or a statistically significantly lower rate of PEP in patients who had a pancreatic stent placed (range 0%-20%) compared with patients in whom a pancreatic stent was not inserted (range 6%-67%). In a meta-analysis of 5 prospective studies involving over 400 high risk for developing PEP patients, the odds ratio of PEP without stent was 3-fold higher than that with stent (15.5% vs. 5.8%; OR 3.2: 95% CI[1.6, 6.4]).[100] In this metanalysis 11.4% of patients developed pancreatitis after ERCP. Statistical analysis disclosed that a pancreatic stent must be placed in 10 patients to prevent one episode of acute pancreatitis. In one study with historical controls, used in the metanalysis, it was found that in 436 patients treated for SOD with biliary sphincterotomy, with or without pancreatic sphincterotomy, the rate of pancreatitis rates was 28.2% (5.4% severe); in those who underwent simple pull-type biliary sphincterotomy without a pancreatic stent vs. 13.5% (0.4% severe) in those who had biliary sphincterotomy, with or without pancreatic sphincterotomy, plus placement of a pancreatic stent ($p < 0.05$); there was a tendency for the rate of pancreatitis to be lower if a pancreatic stent was placed before (10.7%) as opposed to after (19.2%) pancreaticobiliary sphincterotomy.[26] Moreover, it has been shown, that stenting seems to help minimize the severity of pancreatitis in those who develop it .[27,28,30,31] In fact, data from the metanalysis show that among the patients who had pancreatic stent placement, all episodes of post-ERCP pancreatitis were mild in severity [Table 2].

The type and size of pancreatic stents that have been made to reduce the risk of PEP remain nonstandardized.[101] Ideally, the pancreatic stent would be made of soft material, narrow, without flaps, thus allowing pancreatic duct drainage without causing any trauma during placement, while it would spontaneously migrate in the duodenum within a week. After stent insertion, sometimes only of brief duration, pancreatic ductal and parenchymal changes have been observed in approximately one third to two thirds of patients, especially those with previously normal pancreatic ducts. Stents made of newer materials that are softer than the traditional polyethylene and with smaller inner flanges will probably cause less duct injury, although this has not been established.

Ductal changes have been observed mostly with traditional flanged 5F or 7F stents, which may be of similar diameter to the pancreatic duct, are made of rigid polyethylene, and have large pointed inner flanges, all factors that may be injurious to the duct, including injury that occurs during stent removal.[27] Therefore, pancreatic stents used for this purpose are narrow [3-5 Fr in diameter] and short [5 cm in length, or less]. A recent study found that unflanged, longer 3F stents with a single duodenal pigtail were associated with a substantially lower frequency of ductal changes (24%) compared with 5F and 6F stents (80%) and were not observed to migrate proximally into the duct.[102] Insertion of a 3F stent was also associated with a slightly lower rate of PEP (7.5%) compared with a 5F (9.8% pancreatitis) or a 6F stent (14.6%).

Pancreatic injury may be related to the duration of time the stent remains in place; therefore, it is necessary either to document passage of a pancreatic stent with a plain abdominal radiograph or to remove it endoscopically, preferably within 2 weeks if placed as a prophylactic measure. The rate of spontaneous passage of a 3F, unflanged

Table 2. Prospective controlled trials comparing pancreatic stent vs. no stent for the prevention of post-ERCP acute pancreatitis

Study, year	Sample size	High risk population	PEP Stent group	PEP No stent group	OR
Smithline, 1993	93	Yes	6/43	9/50	0.73 (0.25, 2.27)
Sherman, 1995	104	Yes	1/46	8/58	0.13 (0.017,1.15)
Tarnasky, 1998	80	Yes	3/41	10/39	0.07 (0.01, 0.59)
Aizawa, 2001	130	No	0/38	6/92	0.17 (0.009, 3.14)
Fazel, 2003	74	Yes	2/38	10/36	0.14 (0.02, 0.71)

pancreatic stent has been shown to be substantially higher (86%) than that for traditional 4F to 6F stents (65%-73%) ($p < 0.001$). [102] Placement of nasopancreatic drains has been proposed as an alternative to the pancreatic stent, because the former can be removed without an endoscopic procedure. Nasopancreatic catheters are of a relatively large diameter (4F or 5F), while some are flanged, thus a concern for possible ductal injury is raised when they are placed in the relatively narrower duct in the body or in the tail of the pancreas. Moreover, overnight hospitalization is required.

Ironically, attempts at pancreatic stent placement may cause pancreatic trauma. If attempts at pancreatic stent placement fail, the risk of PEP is extremely high.[103] Moreover, it may be difficult to decide which patient and which procedure warrant pancreatic stent insertion. Brackbill et al[101] conducted a survey to assess the current practice patterns of expert biliary endoscopists regarding prophylactic pancreatic duct stents. Prophylactic PD stents were used by 96% of respondents. Stent use was universal during ampullectomy and pancreatic sphincterotomy. Most also used stents for minor papillotomy (93%) and sphincter of Oddi dysfunction (SOD) confirmed by manometry (82%). Endoscopists disagreed on the following: pre-cut sphincterotomy, prior post-ERCP pancreatitis, suspected SOD, and traumatic sphincterotomy. Endoscopists used straight stents, pigtail stents, or a combination. Internal flanges were always used by 14%, never used by 54%, and sometimes used by32%. Recently, Das et al[104] published a cost effectiveness analysis to evaluate the most cost-effective strategy for preventing post-ERCP pancreatitis where they showed that pancreatic-stent placement for the prevention of post-ERCP pancreatitis in high-risk patients is a cost-effective strategy.

Guidewire cannulation

Guidewire cannulation has been proposed as a simple way to avoid PEP.[105] In this technique, the biliary or the pancreatic duct are not selectively catheterized after contrast injection but rather cannulated with a guidewire inserted through a catheter or a sphincterotome. Since selective catheterization is often achieved without previous duct opacification, guidewire cannulation possibly reduces the risk of PEP by minimizing the risk of hydrostatic injury to the pancreas. Michopoulos et al[105] reported a success rate of 95% in deep cannulation of the bile duct with the use of a hydrophilic guidewire. PEP was reported in 2.3% of patients. Lella et al[106] also reported a significant risk reduction for PEP by using a hydrophilic guidewire in selective catheterization of the bile duct with a reported success rate over 97%. This was a prospective randomized trial, with all procedures performed by the same endoscopist and in the study design a power analysis was conducted for detecting differences at the 5% level of significance. Although this study's results were encouraging, this technique was not studied in a high risk population group and more data are needed.

Suggestions and novelties in post ERCP pancreatitis prophylaxis

Post-ERCP pancreatitis has been traditionally considered the most feared and unpredictable complication, with no realistic strategy for its avoidance. Patient related and technical factors have long been recognized to be important in causing post-ERCP pancreatitis. Prevention of post ERCP pancreatitis is feasible when careful patient selection (avoiding unnecessary or inappropriate ERCP), meticulous endoscopic technique, and insertion of a pancreatic stent in selected patients are combined. Traumatic manipulation of the papilla along with the number and the volume of injections of contrast medium into the pancreatic duct should be kept to a minimum. Pancreatic injection should be avoided entirely if there is no indication for pancreatic duct visualization. In case of difficult cannulation, instruments to facilitate, such as tapered tipped cannulas, sphincterotomes, guidewires, and/or placement of a pancreatic guidewire to assist biliary cannulation, should be used in rapid succession. Balloon dilation of the intact biliary sphincter for stone extraction should be avoided in routine practice and pure-cut electrosurgical current, or adjustment of an automated generator to a lower tissue effect, is preferred. Biliary stents, even for hilar tumors, should not be pushed through an intact sphincter. When placing a plastic biliary stent, care should be taken to ensure that the distal flange does not push against the pancreatic duct orifice.[107]

Independently of the technique-related risk factors, operator experience also seems to be a potential risk-factor for post-ERCP/ES complications although most multicenter studies have failed to show a significant correlation between endoscopist ERCP case volumes and pancreatitis rates.[3,4,108] It is possible that none of the participating endoscopists in those studies reached the threshold volume of ERCP above which pancreatitis rates would diminish (perhaps greater than 250-500 cases per year).[107] However, the reported rates of pancreatitis from the highest volume tertiary referral centers in the U.S. are often relatively higher than those in private practices.[3,4] This finding is in consistence with data from a large Italian multicenter prospective study[8] that showed significant differences in the outcome of ERCP between low- (less than 200 ERCPs/year) and large- (more than 200 ERCPs/year) vol-

ume centers. Large-volume centers had significantly less overall complications (2.0 % vs. 7.1 %, P<0.001) and less complication-related deaths (0.18 % vs. 0.75 %, P<0.05), while the risk of pancreatitis was significantly increased in low-volume centers in the univariate analysis (relative risk 2.8).

Pancreatic stent placement appears promising as a strategy for prevention of PEP, one that has dramatically altered outcomes for high-risk patients undergoing ERCP. It is unclear whether this technique will achieve similar benefits when performed by non experienced hands. Most non-tertiary center endoscopists and endoscopy units are unfamiliar with the techniques and equipment needed for placement of pancreatic stents, especially the small diameter guidewires (0.018-0.025 inch) used to place the smaller 3F and 4F stents that appear to be optimal for avoiding ductal injury and for preventing pancreatitis. Specific training in techniques for pancreatic stent placement is recommended.[102]

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