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TOPIC HIGHLIGHT

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Early successes and late failures in the prevention of post endoscopic retrograde cholangiopancreatography

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Abstract

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). The only way to prevent this complication is to avoid an ERCP all together. Because of the risks involved, a careful consideration should be given to the indication for ERCP and the potential risk/benefit ratio of the test. Once a decision to perform an ERCP is made, the procedure should be carried out with meticulous care by an experienced endoscopist, and with a minimum of pancreatic duct opacification. Several pharmacologic agents have been tested, but to date the most important method of reducing post ERCP pancreatitis is the placement of pancreatic stent. Pancreatic stents should be placed in all patients at high risk of this complication such as those undergoing pancreatic sphincterotomy, pancreatic duct manipulation and intervention, and patients with suspected sphincter of Oddi dysfunction. Pancreatic stents should be also considered in patients requiring precut sphincterotomy to gain biliary access.

Key words: Post endoscopic retrograde cholangiopancreatography pancreatitis; Somatostatin; Gabexate; IL-10; Pancreatic stents; Aspirating catheter; Sphincter of Oddi dysfunction

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INTRODUCTION

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), with an incidence of 4% in low risk patients and 40% in high risk patients[1-3]. Most patients experience mild pancreatitis, while severe disease with pancreatic necrosis, multiorgan failure, prolonged hospitalization, and death is seen in 0.3%-0.6% of patients[4,5].

Risk factors for post ERCP pancreatitis can be categorized into patient-related, operator-related, and procedure-related factors. Patient-related factors include young age, female sex, preexisting pancreatitis, prior post ERCP pancreatitis, small/nondilated bile duct, pancreas divisum, lack of chronic pancreatitis, and sphincter of Oddi dysfunction[6]. The principal operator-related factors are low volume and the total number of ERCP's performed annually-both for the endoscopists and the center, but these are controversial as independent predictors of risk. In general, endoscopists who perform more than 2 ERCP's per week have significantly greater rate of successful cannulation. In one study, conducting less than 40 sphincterotomes per year predicted the development of post ERCP pancreatitis[4]. Procedure-related factors include time taken for cannulation, precut sphincterotomy, pancreatic or minor papilla sphincterotomy, pancreatic brushings, acinarization during pancreatogram, number of pancreatic contrast injections, nasobiliary tube placement, and poor drainage of contrast[4]. The various independent predictors may have an additive effect. In view of these observations, choosing the right patient, with the right indication, at the right endoscopy center is essential for the prevention of post ERCP pancreatitis.

The most obvious way to eliminate the risk of post ERCP pancreatitis is to avoid an ERCP entirely. Excellent alternative imaging modalities that are safer such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) are available. A detailed discussion of the diagnostic merits of ERCP, MRCP and EUS is beyond the scope of this review.

Unfortunately, even if the patient has been properly selected and the procedure performed with meticulous technique, pancreatitis can still occur. The mechanisms of post ERCP pancreatitis are incompletely understood.

Hyperamylasemia develops in up to 70% patients, yet only a fraction of patients develops clinical pancreatitis. Several hypothetical mechanisms for post ERCP pancreatitis include pancreatic sphincter hypertension, local edema due to mechanical trauma, electrical injury from electrocautery, hydrostatic or osmotic injury to the acini[7], and contrast-induced activation of proteases leading to oxidative damage to the pancreas[8].

Because ERCP is associated with a high rate of complications, including lawsuits[9], several pharmacological agents and other interventions have been examined in the prevention of post ERCP pancreatitis. The first such trial was published in 1978[10]. The preventive measures used can be categorized as sphincter relaxants, protease inhibitors, types of contrast, anti-inflammatory/anti-oxidant agents, anti-secretory compounds, electrosurgical techniques, and placement of various types of stents. With few exceptions, a positive beneficial response has been rare. Most trials have been small, single-center studies with unexpectedly high rates of post ERCP pancreatitis in the placebo group. Unfortunately, many promising preliminary studies are followed by larger, multicenter trials, which were negative. Sadly, despite several decades of intense investigation and hundreds of published trials, 39 from 2000-2006 alone, other than pancreatic stenting, we still lack an agent with proven benefit in the prevention of post ERCP pancreatitis[11].

PHARMACOLOGIC AGENTS

Hormones

Somatostatin/octreotide: The most widely investigated compound for prophylaxis against post ERCP pancreatitis is somatostatin and its synthetic, longer acting analogue, octreotide[12]. Both inhibit pancreatic secretion directly as well as indirectly by blocking the release of cholecystokinin (CCK) and secretin[7]. In experimental models, both agents have been shown to alter the cytokine milieu, have anti-inflammatory activity, and protect the pancreatic cells[11,12]. Octreotide has additional advantages: it may decrease proteolysis, reduce intraductal pressure, and is administered subcutaneously, unlike somatostatin which requires continuous IV infusion. However, octreotide may increase the basal pressure and frequency of contraction of the sphincter of Oddi[7], which is why most recent trials delay ERCP by one hour after the administration of octreotide[12]. Whether somatostatin also increases the sphincter of Oddi pressure is controversial[7,13,14].

Studies on the use of octreotide and somatostatin have yielded conflicting results. A meta-analysis published in 2000 showed that somatostatin (12 trials) significantly reduced post ERCP pancreatitis while octreotide (10 trials) did not-all in low risk patients[15]. The same group in a subsequent report, noted that the addition of another randomized controlled trial (this time on high risk patients) reduced the effect of somatostatin to a nonsignificant trend. These workers concluded that the routine use of either agent is not justified[16]. A recent meta-analysis of 11 randomized controlled trials from 2000-2002, on 2270 patients published in an abstract form also did not find any benefit with octreotide and somatostatin, except for somatostatin in patients undergoing sphincterotomy[17]. A more recent meta-analysis found benefit with somatostatin only in the prevention of post ERCP hyperamylasemia, which clearly is of dubious importance. Of practical importance, it should be noted that somatostatin is not available in the U.S.

Thomopoulos *et al* resurrected the use of octreotide, and showed a significant reduction (from 8.9% to 2%) in post ERCP pancreatitis, with high dose therapy (500 mg tid for 24 h before the procedure); the only 2 instances of moderate to severe pancreatitis occurred in the placebo group. The cost per patient was $233 for the drug alone[12] and the number needed to treat to benefit one patient was 13. However, this double blind, randomized controlled trial (RCT) was hampered by a single center design, the inclusion of mostly low risk patients, and by the relatively small sample size of 101, giving an a priori power of only 38%[11]. One can only hope that these results can be replicated in larger multi-center trials.

Li *et al*[18] in a multicenter RCT on 418 patients in China, recently reported that 300 mg IV octreotide started 1 h before and continued 6 h after ERCP significantly reduced post ERCP pancreatitis. Several criticisms have been made on this study, including the high prevalence of stone disease in the study population, a significantly greater use of pancreatic stents in the octreotide group, and significantly more nasobiliary drains in the control group[7].

Secretin: Secretin stimulates bicarbonate secretion by the pancreatic ductal epithelium and may relax the sphincter of Oddi. It is often used during ERCP to facilitate cannulation[19]. A retrospective, single center study, published in abstract form, compared secretin use in 141 patients with 4323 controls; post ERCP pancreatitis was virtually nonexistent in the secretin group *vs* 3.6% in the control group[20]. However, an earlier RCT showed that secretin did not reduce post ERCP hyperamylasemia[21].

Glucagon: Glucagon suppresses pancreatic exocrine secretion in animals and humans[22]. It also relaxes smooth muscles, possibly of the sphincter of Oddi[23]. However, in one human study glucagon failed to show any benefit in the prevention of post ERCP pancreatitis[24].

Calcitonin: In the late 1970's and early 1980's, calcitonin was used in several studies to prevent post ERCP pancreatitis, based on its ability to inhibit amylase synthesis and secretion[25]. However, none of these studies showed any benefit with this compound[26,27].

Sphincter relaxants

Nitrates: The use of two milligrams of sublingual nitroglycerin immediately before ERCP significantly reduced post ERCP pancreatitis (from 18% to 8%) in what was believed to be a low risk population[28].Another study found that a 15 mg transdermal glyceryl trinitrate patch significantly decreased post ERCP pancreatitis, from 15% to 4%[29]. However, both these studies were criticized for the high rate of pancreatitis in the placebo groups. Moreover, as with all drugs that relax the sphincter, anatomical factors such as the angle between the ducts, and stiffness of the papilla were likely important predictors

because of the difficulty of cannulation rather than dilation of the ampulla[30]. Another study on 316 patients using a 5 mg transdermal glyceryl trinitrate patch also did not find a reduction in post ERCP pancreatitis, even in high risk patients[31].

Nifedipine, another sphincter of Oddi relaxant, has also proved to be ineffective[32,33].

These disappointing results led to a trial of spraying topically 10 mL of 1% lidocaine to reduce sphincter of Oddi spasm; there was no reduction in the incidence of post ERCP pancreatitis or difficulty in cannulation compared to placebo[34].

Botulinum toxin: One trial evaluated the use of botulinum toxin, a potent and long acting blocker of acetylcholine release. This compound was injected into the pancreatic sphincter in 26 patients with elevated basal biliary sphincter pressure who underwent biliary sphincterotomy. This single center trial did not find a significant reduction in post ERCP pancreatitis in the botulinum group compared to the sham group (24% *vs* 43%, $P = 0.31$). The authors concluded, based on the high rate of pancreatitis in the sham group, that efforts should be made to protect the pancreatic sphincter in such patients[35]. This study has been criticized for the following 5 reasons: (1) High rate of pancreatitis in the placebo arm, which forced the study to be terminated early. (2) The peak clinical response to botulinum toxin in patients with achalasia and sphincter of Oddi dysfunction occurs after several days and not immediately; an agent designed to protect post ERCP pancreatitis should work much quicker to facilitate emptying of contrast. (3) Injection of a small quantity like 0.25 mL of botulinum toxin is very challenging and can easily involve injection of saline or air. (4) Dual sphincterotomy with pancreatic duct stenting is more cost effective and should be the treatment of choice even in patients with isolated hypertension of the biliary sphincter (with type Ⅲ and arguably type Ⅱ sphincter of Oddi dysfunction)[36]. (5) Use of botulinum toxin should always be accompanied with pancreatic duct stenting (see section below on stenting)[37].

Epinephrine: Epinephrine is believed to reduce the sphincter of Oddi pressure and post procedure edema by decreasing capillary permeability. In a nonrandomized study, there was significant reduction in post ERCP pancreatitis and serum amylase levels in patients undergoing balloon extraction of CBD stones and intraductal irrigation with 40-120 mL of a 1:1 000 000 epinephrine solution. There were several problems with this study: (1) All patients received gabexate infusion (see below)[38] (2) the volume of fluid instilled into the ductal system was very large (120 mL), considering that 2 mL is generally sufficient for a pancreatogram. (3) A more rigorous study is necessary to confirm these findings.

Anti-inflammatory agents

Steroids: The ultimate "shotgun" anti-inflammatory agent, corticosteroids, have been tested in several trials. Some workers have postulated that steroids work by stimulating protease inhibitors such as C1q esterase inhibitor and trypsin inhibitor, thus causing inhibition of phospholipase A2 and suppression of contrast-related reactions. The early successful findings[39,40] were followed by larger, more definitive trials which gave negative results[41,42].

Interleukin-10 (IL-10): IL-10 has been shown to reduce the severity of acute pancreatitis in animal studies[43]. A European study on 144 patients showed a reduction in post-therapeutic ERCP pancreatitis which was greater with a higher dose of 20 mcg/kg given 30 min before ERCP compared to a lower dose (4 mcg/kg) and placebo. However, the incidence of pancreatitis in the placebo group (24%) was higher compared to other studies[44]. A larger trial on 200 patients failed to show any benefit with IL-10 given in a dose of 8 mcg/kg, 15 min before ERCP[45].

Some investigators have assessed the effect of adding T-cell suppressants, such as 5FU, to the contrast material used during ERCP. 5FU significantly reduced post ERCP pancreatitis from 10% to 2.5%, and the frequency of hyperamylasemia. However, it is unclear why a drug which causes chronic suppression of cell proliferation would act so quickly[46].

NSAIDs: In a randomized controlled trial on 220 patients, a 100 mg single rectal dose of the nonselective NSAID, diclofenac significantly reduced post ERCP pancreatitis compared to placebo. The protective effect may be related to the inhibition of phospholipase A2, prostaglandins, or neutrophil attachment to the endothelium[47]. One criticism of the study was the lack of response in patients who need prophylaxis the most-those with suspected sphincter of Oddi dysfunction. However, it should be noted that the initial successful outcome in small, single center studies is often negated in larger multicenter trials[48]. Another predicament is that many NSAIDS have been implicated in drug-induced pancreatitis[49]. Interestingly, in a retrospective study from Denmark, diclofenac had the highest risk of drug-induced pancreatitis compared to other NSAIDs[50].

Heparin: A prospective study on the risk factors for post ERCP pancreatitis showed that unfractionated heparin may be protective, but unlike low molecular weight heparin, may increase the risk of post sphincterotomy bleeding[51]. In addition, animal models of acute pancreatitis have shown unfractionated heparin to be anti-inflammatory. However, a randomized controlled trial showed no difference in post ERCP pancreatitis between placebo and certoparin given in DVT-prophylaxis doses, 2 h before and 24 h after ERCP[52].

Anti-oxidants

Allopurinol: It has been postulated that allopurinol by inhibiting xanthine oxidase reduces damage caused by free radicals, thus protecting against the development of post ERCP pancreatitis. In several single center studies, one of which included 250 patients, allopurinol reduced the incidence of post ERCP pancreatitis[53,54]. However, yet again, a larger multicenter trial on 701 patients failed to show any difference between allopurinol and placebo[55].

N-acetyl cysteine (NAC): Intravenous NAC and selenium are free radical scavengers, but studies in the prevention of post ERCP pancreatitis have been disappointing[56,57].

Beta-carotene: Two grams of oral Beta-carotene reduced the severity, but not the incidence of post ERCP pancreatitis in one small study[58].

Protease inhibitors

Aprotonin: Aprotinin is a serine protease inhibitor which inhibits a wide range of proteases including trypsin. It is a member of the Kunitz family of proteins, now called bikunins and has been used during coronary artery bypass surgery as an anti-fibrinolytic agent. In one study, aprotinin administered intravenously did not prevent post ERCP pancreatitis[59].

C1-INH: In a pilot study, C1-INH, a potent inhibitor of the first step in the complement cascade was given intravenously to 20 patients in a dose of 3000IU 30 min prior to ERCP. There was a significant reduction in post ERCP hyperamylasemia in the C1-INH group compared to the placebo group. This study did not assess the prevention of post ERCP pancreatitis[60].

Ulinastatin: In an uncontrolled study from Japan, ulinastatin a protease inhibitor isolated from human urine was found to show promising results when given as continuous arterial infusion in severe acute pancreatitis[61]. Another Japanese study on 406 patients found a significant reduction in post ERCP hyperamylasemia and pancreatitis in patients administered 150 000U of ulinastatin Ⅳ, compared to placebo[62].

Gabexate: The story of gabexate, a synthetic protease inhibitor which can act on trypsin, phospholipase A2, kallikrein, plasmin, thrombin, and C1 esterase, is a classic example of the efforts made to prevent post ERCP pancreatitis. Gabexate was synthesized in 1977[63] and was first used as a prophylaxis agent against ERCP-induced pancreatitis in 1982[21]. In some studies, gabexate administered Ⅳ over 4 h (300 mg) to 12 h (1 gram started 30 min before ERCP) was found to reduce post ERCP pancreatitis[64,65]. However, other studies failed to confirm these results but a meta-analysis found gabexate to be useful when given for at least 6 h[66]. To further muddy the waters, a subsequent large, multicenter trial on 1127 patients using a 6.5 h infusion period found no difference between gabexate, somatostatin, and placebo[67], and a recent large meta-analysis likewise found no benefit of gabexate[68].

Unfortunately, no pharmacological agent has been shown to definitively reduce the risk of post ERCP pancreatitis. Further studies with NSAIDS and 5FU are needed but are unlikely to be successful.

TECHNIQUES

Several methodological steps can reduce the risk of post ERCP pancreatitis. These include avoiding pancreatic injection with contrast, multiple injections, over injection with acinarisation, precut sphincterotomy and nasobiliary tube placement. In addition to these obvious precautions, several other procedural techniques that can be controlled by the endoscopist have been examined.

First, the use of an aspirating catheter during sphincter of Oddi manometry; aspiration through the distal port of the catheter reduces the risk of procedure-induced pancreatitis[69].

Second, the cannulation technique employed can influence development of post ERCP pancreatitis. A study on 400 patients, randomized to cannulation by standard method or with a soft-tipped Teflon guidewire passed through a 6F double channel sphincterotome resulted in improved rates of cannulation and reduction in pancreatitis in the soft-tipped wire group[70].

Third, the role of electrocautery in causing post ERCP pancreatitis has produced conflicting results. Pure cut cautery (ValleyLab) at 30 W/s may carry less risk of post ERCP pancreatitis than blended current, based on an unblinded but randomized, controlled study[71]. By contrast, a larger Canadian study comparing pure cutting current *vs* blended current (blend-2 at 30 W/*sec*, both ValleyLab), found no difference between the two. Incidentally, the pure-cut group had significantly higher bleeding rates[72]. This led many endoscopists to use pure-cut current initially then switching to blended current to complete the sphincterotomy. However, a study on 186 patients with choledocholithiasis randomized to pure-cut or blended current or pure-cut followed by blended current, using a Plus Ⅱ electrosurgical generator set at 34 Watts/s, showed that blended current may not be the best approach. Development of pancreatitis was significantly less in the pure-cut group (3.2%) compared to the blended current and mixed modality groups (12.9% each). One patient in each group (1.6% each) had post sphincterotomy bleeding[73]. The use of more advanced electrosurgical devices that alter the current from cut to blend depending on the resistance experienced (Endocut, Erbe), did not improve the rate of bleeding or pancreatitis[74,75]. At present, no definite recommendations can be made on the type and settings of the electric current.

Fourth, the type of contrast agent used, with few exceptions, does not have any impact on the post ERCP pancreatitis[76]. However, many of the studies were underpowered. A meta-analysis failed to show any difference in the rate of post ERCP pancreatitis in ionic *vs* nonionic contrast agents[77].

Fifth, it has been hypothesized that patient position after ERCP may facilitate contrast drainage. In a small and unblinded study published as an abstract, 3 patients placed in the supine position after ERCP developed post ERCP pancreatitis, compared to only one patient placed in the right lateral decubitus position; the difference was not significant[78].

Sixth, arguably the use of pancreatic stents has had the greatest success in preventing post ERCP pancreatitis. The first group of workers (at the University of Indiana) to assess prophylactic stenting, found no difference in post ERCP pancreatitis in patients undergoing biliary sphincterotomy, although a trend was observed in the length of hospital stay and severity of pancreatitis in favor of the stented group[79].

Another study from Indiana, this one published in abstract form, addressed the question of whether patients whose ERCP resulted in inadvertent or repeated pancreatic duct cannulation should have a pancreatic stent placed before a precut biliary sphincterotomy. In a large study involving 151 patients those who were randomized to

stent placement (for 7-10 d) had significantly lower rate of post ERCP pancreatitis (2.2%) compared to patients who underwent biliary sphincterotomy without a pancreatic stent (21.2%), and those whose pancreatic stents were removed soon after biliary sphincterotomy (13.8%)[80].

Other trials have obtained similar results. In a study on 80 patients undergoing biliary sphincterotomy for sphincter of Oddi dysfunction because of pancreatic sphincter hypertension diagnosed by manometry, patients randomized to pancreatic duct stenting had a dramatically reduced the rate of post ERCP pancreatitis compared to the control group (7% *vs* 26% with a relative risk reduction of 10.5)[81].

An unblinded but randomized trial of 76 patients at high risk for post ERCP pancreatitis because of predisposing factors such as sphincter of Oddi manometry, sphincterotomy, and prolonged cannulation time (> 30 min), the pancreatic stent group had a significantly lower incidence of post ERCP pancreatitis compared with unstented patients (5% *vs* 28%). Moreover, pancreatitis was less severe in the stented group[82].

A subsequent meta-analysis of 5 trials found a 3-fold reduction in post ERCP pancreatitis in patients who had received prophylactic pancreatic duct stents. The number needed to prevent one episode of pancreatitis was 10[83].

Although some experts have argued that nasopancreatic tubes prevent post ERCP pancreatitis as effectively as stents without the risk of stent-related histological changes in the pancreatic duct[84,85], a study carried out by the Milwaukee group on high risk patients (sphincter of Oddi manometry, excessive papillary manipulation, difficult sphincterotomy) found no difference in the incidence of post ERCP pancreatitis or the length of hospital stay between patients randomized to receive nasopancreatic tube and the control group. However, this study was published only in an abstract form, and the sample size was small (37 patients)[86]. By contrast, a subsequent retrospective review found the rate of post ERCP pancreatitis to be similar in patients receiving nasopancreatic drainage for 24 h compared to pancreatic stenting, both of which were much lower compared to controls. This group typically uses nasobiliary drainage when pancreatic sphincterotomy is the primary procedure, and employ stents when further pancreatic duct intervention is planned[87].

It has been suggested that a 3 French infringed stent should be used as it is associated with a low rate of post ERCP pancreatitis. In addition, after 14 d, 80% of the stents dislodge spontaneously, obviating the need for a repeat endoscopy[88].

Indeed, the greater acceptance of pancreatic stents in North America compared to Europe and Asia has been proposed as an explanation for the variability in results in the post ERCP pancreatitis prevention trials[69].

A recent, large, single center retrospective analysis found that the quantity of pancreatic duct injection was the best predictor of development of post ERCP pancreatitis. The only other independent predictor was sphincter of Oddi dysfunction. Therapeutic ERCP predicted the frequency and severity of post ERCP pancreatitis only in the subgroup in which there was opacification of the pancreatic duct to the tail. Interestingly, patients undergoing pancreatic stenting had a significantly higher rate of post ERCP pancreatitis, although in the subgroup undergoing sphincter of Oddi manometry with opacification to the tail, pancreatic stents did significantly reduce the rate of post ERCP pancreatitis[3].

CONCLUSION

The only sure way to prevent post ERCP pancreatitis is to avoid an ERCP. Therefore, careful consideration should be given to the indications and the risk/benefit ratio before ERCP is performed. Once the decision to pursue ERCP is made, the procedure should be carried out with meticulous care by an experienced endoscopist, and with a minimum of pancreatic duct opacification. To date, the most important measure shown to reduce the risk of post ERCP pancreatitis is the use of pancreatic stents. Pancreatic stents should be placed in patients at high risk of pancreatitis such as those undergoing pancreatic sphincterotomy, pancreatic duct manipulation/intervention, and patients with suspected sphincter of Oddi dysfunction undergoing sphincter of Oddi manometry-especially those whose pancreatic ducts have been inadvertently opacified to the tail. Pancreatic stents should also be considered in patients requiring precut sphincterotomy to gain biliary access. Pancreatic stents should only be placed at a center experienced in interventional ERCP and by a skilled endoscopist. If stenting becomes difficult, the additional manipulation may in some settings outweigh the benefits reported by advanced centers.

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