REVIEW

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Prevention of post-ERCP pancreatitis

Post-ERCP pankreatitin önlenmesi

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INTRODUCTION

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Although post-ERCP pancreatitis (PEP) is reported to occur in 1-40% of cases, in prospective studies, it is reported to occur in 5–7%. In a study including a review of prospective studies (1), PEP occurred in 3.5% of patients. The difference between the incidence rates is due at least in part to different definitions of pancreatitis. PEP is most commonly defined as newly emerging or worsening of prior abdominal pain with a serum amylase level at least three times higher than the upper limits of normal within 24 hours of ERCP. What should be kept in mind is that transiently elevated serum amylase levels alone without abdominal pain (hyperamylasemia) as well as abdominal pain occurring shortly after ERCP due to intestinal gas retention (gastrointestinal smooth muscle dysfunction syndrome) are conditions that may be associated with elevated serum amylase levels and leukocytosis but should not be confused with pancreatitis. If abdominal pain lasts more than 24 hours, contrast-enhanced computerized tomography (CT) is recommended if the diagnosis is in doubt. If the patient has pancreatic-type abdominal pain and leukocytosis, we consider the patient to have pancreatitis and treat based on our clinical experience without obtaining abdominal imaging studies other than a plain abdominal X-ray to exclude a perforation. The severity of pancreatitis is graded according to the prolonged length of stay in the hospital as: mild for hospitalization or prolongation of hospital stay up to 3 days, moderate for prolongation between 3 and 10 days, and severe for prolongation of more than 10 days. More than 90% of PEP is of mild severity and about 10% represents moderate or severe pancreatitis.

Many risk factors contribute to PEP, including patient-related, endoscopist-related and ERCP methods (2). The following are among the described risk factors: young and female patient, known or suspected sphincter of Oddi dysfunction (SOD), small diameter bile duct, normal serum bilirubin, history of acute recurrent pancreatitis, previous PEP, inexperienced endoscopist, difficult cannulation, pancreatic sphincterotomy, multiple pancreatic duct contrast injections, pancreatic acinarization, pre-cut sphincterotomy, balloon sphincteroplasty without sphincterotomy, sphincterotomy using blended current, Oddi manometry, and endoscopic ampullectomy.

The factors playing a role in the pathogenesis of PEP include: mechanical injury resulting from difficult cannulation, hydrostatic injury as a result of excess contrast agent injection to the pancreatic duct, allergic or chemical injury due to ionic contrast agents within the pancreas, enzymatic injury occurring by the activation of enzymes in the intestinal contents, bacterial injury due to contaminated endoscopes and accessories, and finally thermal injury from electrocautery. The final common pathway is premature activation of proteolytic pancreatic enzymes with autodigestion of the pancreas. Inflammatory cytokines released by autodigestion lead to the local and systemic inflammatory response manifested as acute pancreatitis (Figure 1).

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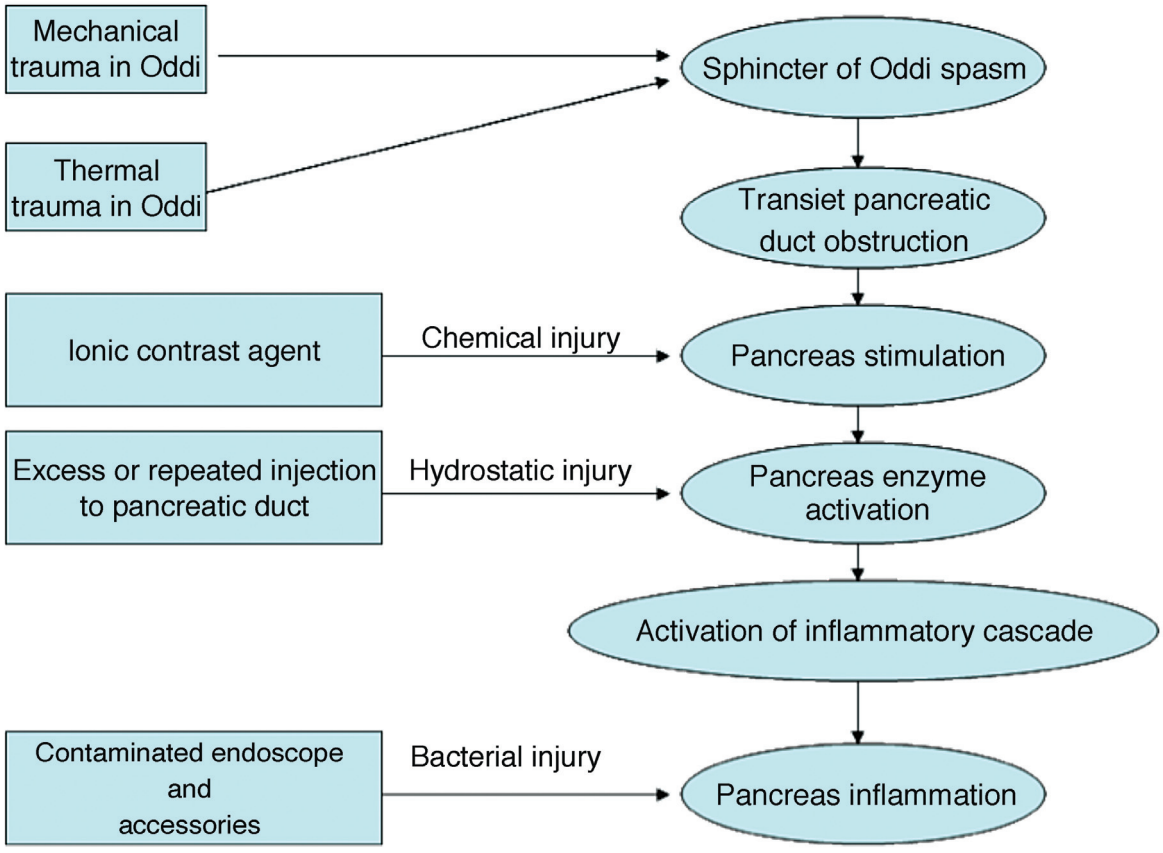

Figure 1. Post ERCP pancreatitis: Pathogenesis

Reduction of the risk factors that play a role in the development of PEP is essential in prevention (3-6). It is impossible to change patient-related risk factors. However, proper patient selection, techniques of cannulation, and endoscopist risk factors can be changed. Despite recent technical developments in ERCP and increase in endoscopy experience, there has not been a dramatic decrease in the incidence of PEP. Several studies have been conducted over the last 15 years involving pharmacological agents and mechanical methods for preventing PEP or decreasing its severity. In this review, the results of these studies will be discussed.

PREVENTION

Patient selection and general measures will be briefly mentioned followed by a discussion of the role of technique and pharmacological prophylaxis based on pathogenesis.

Patient selection and general measures

In patients with abdominal pain who have a low probability of bile duct stones, especially young women, alternative noninvasive or less invasive imaging studies of the biliary tree should be performed. These include magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS). Young female patients, with suspected SOD and a normal choledochus, repeated abdominal pain and normal serum bilirubin levels are at 10 times greater risk for PEP, and those patients should be informed about such risk of pancreatitis. Ideally, such patients should be referred to specialized ERCP centers for ERCP with SOD manometry, if indicated (3). Purely diagnostic ERCPs with contrast injection alone should not be performed in these patients.

General measures should be followed to reduce the risk of PEP. Diagnostic ERCP should be avoided as much as possible, and alternative noninvasive or less-invasive diagnostic methods should be used. The endoscopist and their assistants should be adequately trained, and the endoscopy unit should perform an adequate number of procedures to maintain endoscopist proficiency. Properly disinfected endoscopes and sterilized accessories should be used. An attempt should be made to se-

lectively cannulate the bile duct without undue trauma to the papilla and with avoidance of contrast injection into the pancreatic duct. If the pancreatic duct needs to be opacified, cannulation time and injection number should be limited and acinarization should be avoided. The use of an aspiration catheter for pancreatic duct SOD manometry should be used (3).

Reducing mechanical damage - biliary cannulation techniques

Since mechanical trauma that occurs during difficult biliary cannulation is one of the most important factors for the development of PEP, the technical measures taken to aid in cannulation will decrease the risk for pancreatitis. Difficult cannulation is generally considered as failure of biliary cannulation within 10 minutes or >10-15 attempts at cannulation. Accessories such as use of sphincterotomes, guidewires and catheters and techniques such as early use of pre-cut sphincterotomy and pancreatic guidewire biliary cannulation that facilitate the cannulation can reduce PEP (7).

Guidewire biliary cannulation

Several studies have shown that wire-guided biliary cannulation (guidewire cannulation or GWC) increases the success rate of primary cannulation and significantly decreases the risk of PEP compared to standard cannulation (SC) techniques using contrast alone. In two of several prospective, randomized trials, GWC was performed in 150 patients and SC in 150 patients. PEP developed in 3 and 13 patients (2%, 8.6%) in the GWC group and in 17 and 25 patients (11.3%, 16.6%) in the SC group, respectively (p=0.001, p=0.037) (8,9). In the first of these studies, SOD and female gender were defined as the risk factors for PEP. Three patients had suspected SOD and GWC was not found to prevent PEP in patients with SOD.

In a meta-analysis that evaluated the results of five randomized controlled trials, biliary cannulation rate was achieved in 74.9% using SC techniques. Biliary cannulation was achieved more often with GWC (85.3%) with a significant reduction in PEP (10). In the systemic review and meta-analysis of seven randomized controlled trials (11), PEP occurred in 3.2% of the GWC group and 8.7% of the SC group; the primary cannulation rate was 89% in the GWC group and 78% in the SC group. Pre-cut was required in 2.4% in the GWC group and 21.4% in the SC group. Thus, GWC increases the success of primary cannulation and decreases both the need for pre-cut and the incidence of PEP. Another prospective randomized trial of 413 patients (12) showed that while GWC increased the rate of successful cannulation, it did not decrease the incidence of PEP. However, the technique used in this study likely affected the outcome. The assistant attempted to pass the GW for 5 minutes; if unsuccessful, the endoscopist attempted GW passage for 5 minutes. If unsuccessful, the groups were crossed over. If cannulation was not achieved, the protocol was repeated and pre-cut was performed with a needle-knife sphincterotome (NKS) when biliary cannulation failed. PEP developed in 16/202 patients in the GWC group and in 13/211 patients in the SC group (p=0.48). PEP was found in 29 (7%) of all patients. Successful cannulation was achieved in 81.4% in the GWC group and 73.5% in the SC group before crossover (p=0.03). Female gender, SOD and complete pancreatic duct filling were identified as independent risk factors for the development of PEP. Four or more attempts to cannulate the papilla increased the risk for PEP by more than 10%. In a meta-analysis supporting the results of this study, the results of four randomized controlled trials were evaluated. GWC was not found to significantly decrease PEP compared to SC (13). In another prospective randomized crossover trial (14), GWC and SC were compared. While the initial cannulation rate in the GWC group was found to be significantly higher than in the SC group (p<0.001), cannulation time, PEP incidence and other complication rates, and rates of pre-cut did not differ between the two groups.

Several studies have shown that short-length GWs controlled by the endoscopist shorten procedural time, decrease trauma at the papilla and reduce PEP. In a prospective randomized trial (15), using short GWs, the mean exchange time was 125 seconds in the short GW group and 177 seconds in the long GW group (p=0.05). PEP developed in 1 patient in the short GW group and in 2 patients in the long GW group. In another retrospective cohort study (16), cannulation with a physician-controlled GW was performed in 76 patients. Cannulation was successful in 71 (93%) patients. Biliary cannulation was performed without need for pre-cut in 60 (78.9%) of these patients. PEP occurred in 4 (5.3%) patients, pre-cut was needed in 15 patients, and bleeding occurred in 2 (13%) of these. However, the results of initial studies have not been published. Further randomized

controlled trials of large volumes and meta-analyses are necessary on this subject.

Pre-cut sphincterotomy

Pre-cut biliary sphincterotomy is used for difficult biliary cannulation, increases biliary cannulation success, and is commonly assumed to cause an increase in the risk for PEP. However, it is not clear whether the increase in PEP is due to prolonged attempts at cannulation prior to the use of pre-cut. In two randomized prospective trials, pre-cut was needed for biliary cannulation in 94 (12.8%) of 732 patients with native papillae. Biliary cannulation was achieved using pre-cut NKS in 80 patients (85%). PEP was seen in 14 (14.9%) of these patients and in 39 (6.1%) of 638 patients without the need for pre-cut ($p<0.01$). The number of attempts at cannulation of the papilla increased the risk of PEP. Pancreatic duct stent placement was undertaken in 22 patients, and PEP developed in 5 patients. While female gender, partial pancreatic drainage and more than 10 attempts to cannulate the papilla were identified as independent risk factors for PEP, NKS was not found to be a risk factor. All episodes of pancreatitis were mild, and there were no episodes of perforation or bleeding (17). In a randomized comparative trial, patients with failed cannulation were divided into two groups: early NKS was used in one group (32 patients), and continuation of SC for 15 minutes was used in the other group (30 patients). Successful biliary cannulation and complication rates were similar in the two groups. The low numbers of patients is considered to be a major limitation of the study (18). In another study comparing needle-knife pre-cut fistulotomy and standard pre-cut, PEP and hyperamylasemia were found significantly lower in the fistulotomy group than the standard pre-cut group (0%, 7.6%, $p<0.05$; 2.7%, 17.7%, $p<0.01$, respectively), although there was no difference in other complications (19). In a prospective randomized trial of 146 patients, the timing of pre-cut (20) was studied. Pre-cut was directly introduced in 36 patients, and was used in 110 patients following attempted SC for 20 minutes. Successful biliary cannulation was achieved in 92% in the pre-cut group and in 70% in the SC group. Pre-cut was performed in 32 patients of the SC group and biliary cannulation was achieved in 26 patients, and the biliary cannulation rate increased to 95%. Complications were seen in 3 (8%) patients from the direct pre-cut group and in 7 (6%) patients in the SC and delayed pre-cut group. In a meta-analysis of six studies that included 966 patients, there was no difference in successful biliary cannulation (90%) between the early pre-cut and SC groups. PEP occurred in 2.5% in the early pre-cut group and in 5.3% in the SC group. Other complications occurred at a similar rate, and early pre-cut was shown to decrease the risk for PEP (21). However, pre-cut is a technique that requires experience for high success and low complication rates. We believe that in the hands of experienced biliary endoscopists, pre-cut is a useful method for achieving biliary cannulation. In our practice, we apply pre-cut if deep biliary cannulation is not achieved after several attempts using a GW. We perform fistulotomy with NKS or from the orifice and try to reach the choledochus by cutting the papillary roof in the 11 o'clock direction.

Pancreatic guidewire-assisted biliary cannulation

This technique is performed in cases of difficult biliary cannulation. Biliary cannulation is then attempted after insertion of a GW into the pancreatic duct to prevent undesired pancreatic duct cannulation. A pancreatic stent must be placed at the end of the procedure to prevent PEP. In a multicenter study of 188 patients, cannulation was attempted using both pancreatic and biliary GWs (dual GW system) in 97 patients, and SC attempt was continued in 91 patients. Successful biliary cannulation and PEP rates were at 47% and 56% and 17% and 8% in the two groups, respectively. The authors underlined that the dual GW system might be associated with a higher risk of PEP. However, the limitation of the study included the quantity and number of contrast injections into the pancreatic duct (22). In another randomized controlled trial with 107 patients, biliary cannulation could not be achieved in 10 minutes with SC in 53 patients. These cases were then randomized into two groups. Biliary cannulation was attempted with pancreatic GW assistance in 27 patients and with continued SC in 26 patients. The successful cannulation rate was 93% in the pancreatic GW group and 58% in the continued cannulation group. PEP did not occur in either group (23). In a retrospective analysis that included 113 patients, biliary cannulation was achieved in 73% and PEP in 12% in the pancreatic GW-assisted cannulation. PEP occurred in 4.7% of the patients in whom a stent was placed compared to 22% in those without stent placement (24). Lack of pancreatic stent placement was found to be a major risk factor for

PEP when using pancreatic- assisted biliary cannulation. When pancreatic GW-assisted biliary cannulation is performed, it likely facilitates biliary cannulation by straightening the tortuous common channel and stabilizing the papilla, raising it upward to prevent repeated contrast injection into the pancreatic duct, and allows for pancreatic duct stent placement at the end of the procedure.

Reducing thermal damage - current selection

Electrocautery causes edema around the pancreatic orifice, which then prevents pancreatic drainage. Pure cutting current is felt to reduce edema following sphincterotomy, thereby reducing the incidence of PEP. However, an incision using pure cutting current increases the risk of bleeding. In a randomized trial comparing pure cutting and blended currents, 12 (14%) of 16 complications developed with blended current and 4 (5%) with pure cutting current ($p<0.05$). PEP was seen in 10 patients (7 mild, 2 moderate, 1 severe) in the blended group and in 3 patients (all of them mild) in the pure cutting group (25). In a prospective randomized controlled trial, including a larger number of patients, there was no difference between pure cutting and blended currents in terms of PEP (7.8% vs. 6.1%, $p=0.62$). Minor bleeding occurred more often in the pure cutting group (26). In a study of two currents used sequentially, there was no difference between the group in which the incision was started with pure cutting and completed with blended compared to performing the entire incision using the pure cutting in terms of PEP; visible intra-procedural bleeding episodes occurred significantly more often in the pure cutting group (41% vs. 23%, $p<0.05$) (27). In a randomized prospective trial comparing pure cutting current and blended currents sequentially compared with pure cutting and blended currents alone, PEP occurred in 3.2% in the pure cutting group, 12.9% in the blended current group and 12.9% in the pure cutting and blended sequentially group. In that study, the PEP rate with pure cutting was significantly lower than in the other two groups ($p=0.048$); bleeding was seen in 1 patient from each of the three groups (28). In a meta-analysis of four prospective randomized trials including 804 patients, PEP occurred in 3.8% of the pure cutting group and 7.9% of the blended current group. The difference was not statistically significant. Bleeding was seen in 37% in the pure cutting current and 12% in the blended current group (29). Consequently, it is believed that the type of current does not affect the incidence of PEP. Furthermore, pure cutting current increases the risk of bleeding. Therefore, blended current is safe for sphincterotomy, particularly in the patients with a high risk of bleeding.

Reducing chemical or allergic damage - contrast agent selection

Although low osmolarity non-ionic contrast agents are considered to decrease the incidence of PEP, this has not been proven in published studies. In one study investigating the incidence of PEP, PEP occurred in 10.4% when ionic contrast was used and in 10% when non-ionic contrast was used; thus, the non-ionic contrast agent did not decrease the PEP incidence (30). In a meta-analysis of the clinical studies of contrast agent use, no significant difference in PEP was found between low and high osmolality contrast agents (31). In addition, the effects of ionic and non-ionic contrast agents on pancreas tissue were investigated in a canine model. No difference was found between the groups in terms of hyperamylasemia, leukocytosis and cellular damage (32).

Mechanical reduction of pressure in the pancreatic duct – pancreatic duct stent placement

Impairment of pancreatic drainage appears to be crucial in PEP pathophysiology. When there is a mechanical problem, the solution is also often mechanical. The incidence and severity of PEP decrease after pancreatic stent placement in patients at high risk for PEP. These include patients with known or suspected SOD, pancreatic sphincterotomy or pancreatic endotherapy, pre-cut sphincterotomy and ampullectomy, and those with pancreatic GW-assisted biliary cannulation (33,34). Pancreatic stent placement is the only method that can be performed on demand to prevent PEP in high-risk patients. While a large amount of data is accumulating on this subject, there are unanswered questions. These include the duration a stent should remain in place to be effective, the damage it may cause to the pancreatic duct, spontaneous dislodgement or removal of the stent, and the stent design (35). In four (36-39) fully published works and two abstracts, totaling six prospective randomized controlled trials, the rate of PEP significantly decreased following pancreatic duct stent placement (40,41). In two case-controlled trials (42,43) and one retrospective

analysis (44), pancreatic stent placement decreased the incidence of PEP. In one survey, the PEP rate did not decrease with stent placement, but moderate and severe pancreatitis were seen less often in patients in whom a stent was inserted (45). In a meta-analysis (46) of five controlled studies, PEP incidence was found to be one-third lower in patients in whom a stent was inserted compared to patients with no stent insertion (5.8% vs. 15.5%; p=0.001). In a subsequent meta-analysis of six controlled and 12 uncontrolled studies, PEP incidence was found to be 16.5% in the patients without stent placement. PEP risk was significantly lower in the stent group than controls (odds ratio [OR]: 0.44, 95% confidence interval [CI]: 0.24-0.81). Definite risk reduction was defined as 12.0 (95% CI: 3.0–21.0), and the number required for the treatment as 8 (95% CI: 5-34) (47). The importance of pancreatic stent placement further increases in high-risk groups. In one study, a pancreatic stent was implanted in 22 patients who underwent needle-knife fistulotomy for difficult biliary cannulation. These patients were compared with 35 patients in a similar condition but without stent placement. PEP did not occur in any of the patients in whom a stent was placed. PEP rate occurred in 43% in those without stent placement (48). In a more recently conducted randomized controlled multicenter study, PEP incidence was found to be significantly lower in the patients in whom a stent was placed (3.2%) compared to those without stent placement (13.6%) regardless of the risk factors for PEP (p=0.019). In this study, the stents were 5F diameter and 3 cm in length, flat and unflanged. The success of stent placement was 96%, the spontaneous stent dislodgement rate was 95.7%, and mean stent dislodgement time was 2 days (49). However, pancreatic stent placement is not completely without risk despite its efficiency in the prevention of PEP. The morphological changes in the normal pancreatic duct and parenchyma caused by a stent may be irreversible and may lead to serious clinical outcomes (50,51). The stent is expected to spontaneously dislodge in 7 to 10 days. Stents that are shown to not dislodge on abdominal X-ray should be removed within two weeks to prevent ductal and parenchymal changes. Short stents without internal flaps are recommended because of their ease of placement, high spontaneous dislodgement rates and less ductal changes. In a randomized controlled trial (52), 116 patients with stent of 3 cm in length and 5F diameter were compared with patients in whom a stent of 8 cm in length and 3F diameter was placed. Successful stent insertion was 100% in the short stent group but failed in 11 patients in the long stent group (p=0.003). Spontaneous stent dislodgement at two weeks was found in 98% in the short stent group and in 88% in the long stent group (p=0.001). Although PEP incidence was lower in the short stent group, the difference (9% vs. 14%) was not statistically significant. In a retrospective study (53), unflanged pancreatic stents ranging from 3-6F in diameter were placed during 2,447 ERCPs in 2,283 patients. Indications for stent placement were predominantly SOD, pancreas divisum treatment and pre-cut sphincterotomy. ERCP was repeated and pancreatic ductal changes were evaluated in 479 patients. PEP rates with 3F, 4F, 5F, and 6F stents were found to be 7.5%, 10.6%, 9.8%, and 14.6%, respectively (3F vs. 4F, 5F, 6F: p=0.047). Spontaneous stent dislodgement rates were 86%, 73%, 67%, and 65% (3F vs. 4F, 5F, 6F: p<0.0001). Ductal changes occurred in 24% of the patients with 3-4F stents implanted compared to 80% in those with 5-6F stents. In another study (54), duodenal pig-tail stents were compared with flapped stents. PEP incidence was found as 3% in the pig-tail group and 13.6% in the flapped group (p=0.019), and the spontaneous dislodgement rate was 95.4% in the pig-tail group and 81.8% in flapped group (p=0.007).

Although pancreatic stent placement is successful in the prevention of PEP, its application is not technically easy, particularly in those with a stenotic pancreatic orifice or in small or tortuous ducts. Many of the experienced centers report insertion failure rates between 5–10% with the standard method. Moderate or severe pancreatitis developed in two-thirds of the failed insertion patients compared to 14.4% when the procedure was completed with a 0.018 inch GW and 4F, 2 cm stent (55).

Prophylactic stent placement is cost-effective in the patients at high risk but not in those with moderate or low risk for PEP. PEP rates of up to 65% occur when stent placement failed. Therefore, prophylactic stent placement is cost-effective if the insertion success rate is more than 75% in high-risk patients (56). In a study on the use of pancreatic stent placement in practice to prevent PEP (57), a questionnaire was sent to 54 experienced endoscopists, and 49 (91%) of them responded. Of the responders, 96% had used pancreatic duct stents. The stents were placed following ampullec-

tomy and pancreatic sphincterotomy. The majority of them placed stents in patients with minor papillotomy (93%) and SOD confirmed by manometry (82%). The endoscopists disagreed on pancreatic stent placement following pre-cut sphincterotomy (71%), and in patients with a prior history of PEP (64%), suspected SOD (58%-69%) and traumatic sphincterotomy (44%). Of the endoscopists, 33% used flat, 30% pig-tail and 33% a combination. Of them, 14% always, 54% never and 32% occasionally used internal flanges. Diameter and length of stents, time to keep the stent in place and removal methods were highly variable. In conclusion, endoscopists seemed to agree on the implementation of prophylactic pancreatic stents in patients at high risk for PEP. However, there are numerous variables in the stent placement methods and patient selection.

Pharmacological prophylaxis

Despite numerous studies on pharmacological prophylaxis since PEP was first described, a drug with clearly proven efficacy in preventing PEP has not been identified. Many studies with contradictory results involving somatostatin, octreotide, corticosteroids, interleukin (IL)-10, gabexate mesilate, ulinastatin, heparin, glyceryl trinitrate, allopurinol, nifedipine, diclofenac, secretin, botulinum toxin, lidocaine, epinephrine spray, and antibiotics have been published. Drugs are selected based on the proposed pathophysiological mechanisms of PEP. However, the "therapeutic window" is short due to the time between ERCP and onset of pancreatitis at only a few hours, and drugs should prevent PEP or decrease its severity in that short time. According to the pathogenesis, the drugs can prevent PEP by: 1) reducing sphincter of Oddi pressure, 2) reducing pancreatic stimulation, 3) inhibiting protease activity, 4) blocking the enzyme-mediated pancreatic inflammatory cascade, and 5) reducing systemic inflammation (58,59).

Drugs that reduce sphincter of Oddi pressure

Reduction of sphincter of Oddi pressure may prevent PEP by providing pancreas drainage. Results of studies conducted with nitroglycerin, nifedipine, epinephrine or lidocaine spray, and botulinum toxin injection are contradictory.

Nitroglycerin (glyceryl trinitrate, NTG) is a quick and short-acting organic nitrate used in cardiovascular disease with a strong relaxant effect on the smooth muscles. It can be administered sublingually, transdermally or intravenously (IV). It reduces sphincter of Oddi pressure to a basal level within 15 minutes after administration. Two major side effects are hypotension and headache. Transdermal use is preferred due to a lower incidence of side effects. In a trial of 144 randomized patients, placebo-controlled NTG was administered transdermally with 15 mg/24 hours (60). Although PEP incidence and hyperamylasemia significantly decreased compared to placebo (4.2% vs. 15.1%, $p<0.05$), in a multicenter study (61) of 820 patients, PEP occurred in 4.5% of 402 patients in whom NTG was administered transdermally compared to 7.1% of 405 patients who received a placebo; the difference was not statistically significant ($p=0.11$). Severe headache and hypotension were seen significantly more in the NTG group ($p<0.001$, $p=0.006$, respectively). In a meta-analysis examining the effect of NTG (62), it was administered transdermally in three of five randomized controlled trials, and a statistical reduction in PEP was not reached. Of two recent meta-analyses, discordant results were seen. In the first meta-analysis, which included 1,920 patients and eight studies (63), PEP occurred in 5.9% of the NTG group and in 9.8% of the control group ($p=0.002$); NTG reduced the risk of PEP by 40%. The authors emphasized that the optimal dose, route of administration and timing were undefined and required further studies. The second meta-analysis (64) included 856 patients from four studies published in 2010. When considering all PEP cases, it was found to be significantly lower in the NTG group than placebo ($p=0.02$), but when the cases were divided into two groups as moderate and severe PEP, there was no difference between the two groups. In addition, there was also no difference in terms of PEP incidence when subgroup analysis was performed as to high and low risk for PEP. While hypotension was encountered in half of the NTG group, this rate was 5% in the placebo. In conclusion, with respect to the efficacy of NTG in preventing PEP in high-risk groups and in preventing moderate or severe pancreatitis, the evidence is insufficient. In addition, there is a high rate of hypotension when used.

Nifedipine, a calcium channel antagonist, administered 3 hours before and 6 hours after ERCP was not effective in reducing PEP (65). The efficacy of topical administration of lidocaine on the papilla in the prevention of PEP has not been established (66). Topical administration of epinephrine on the papilla was evaluated in three studi-

es (2 prospective and 1 retrospective). In the first study, epinephrine was found to prevent PEP (1.2% vs. 7.6%, p<0.05) (67). However, its effectiveness was not found to be statistically significant in two other studies (68,69). Botulinum toxin injection into the pancreatic sphincter after biliary sphincterotomy was studied in a small patient group with SOD. PEP decreased numerically but not statistically compared to the sham group (70).

Drugs reducing pancreatic enzyme secretion

Antisecretory drugs prevent PEP by inhibiting the secretions of the exocrine pancreas that cause autodigestion of this organ. Somatostatin and its synthetic analog octreotide are the potent inhibitors of exocrine secretion. Besides the antisecretory effects, they have anti-inflammatory and cytoprotective effects (71,72). Somatostatin is believed to decrease sphincter of Oddi pressure, and octreotide increases the basal pressure in the sphincter (73,74). However, in a clinical study of 15 cholecystectomized patients, somatostatin was administered in 6 and octreotide in 9 patients. Flow in the sphincter of Oddi was shown to slow in both groups, and both drugs increased the sphincter of Oddi pressure (75). The efficacy of somatostatin and octreotide in prevention of PEP was studied in several randomized controlled trials. In two randomized controlled trials conducted by the same author before and after 2000, somatostatin significantly increased PEP incidence compared to placebo (9.9% vs. 2.2%; 13.3% vs. 4.4%, p=0.01) (76,77). In the second study, somatostatin was administered just before and after ERCP in a single bolus dose of 250 µg (77). In another randomized controlled study conducted after 2000, somatostatin significantly decreased PEP incidence compared to placebo (9.8% vs. 1.7%; p≤0.05) (78). In a comparative study, neither somatostatin nor gabexate maleate (GM) was found to be superior to placebo in the prevention of PEP (79). In a recent randomized controlled trial, somatostatin significantly decreased PEP incidence compared to placebo (3.6% vs. 9.6%, p=0.02) (80). The first of the two meta-analyses conducted by the same author was performed in 2000 according to the results of randomized controlled trials. Somatostatin significantly decreased PEP, abdominal pain and hyperamylasemia compared to controls (p<0.001, p<0.001, p=0.008) (81). However, in the second study performed in 2007, including the meta-analysis of nine randomized controlled trials, somatostatin did not decrease PEP incidence (5.3% vs. 7.3%), but hyperamylasemia was seen less often with somatostatin. While there was no difference between the short or long infusion, it was felt to be more effective when administered as a bolus (82). In a more recent meta-analysis, 17 randomized controlled trials with the results of 3,818 patients were evaluated. Infusions lasting longer than 12 hours, somatostatin administered as a bolus and in a high dose, somatostatin injection into the pancreatic duct, and biliary sphincterotomy were defined as good indicators for the prevention of PEP (83). Thus, the results of these meta-analyses are inconsistent. Administration route, time and dose are still unclear. Moreover, administration of an expensive drug to all patients is not cost-effective. Administration on demand in the high-risk group does not seem possible today due to uncertainties in the treatment schedule.

Octreotide is a long-acting somatostatin analogue. Its advantage is ease of use, as it is administered subcutaneously. In six randomized controlled trials conducted up to 2001, octreotide was administered subcutaneously or by IV bolus in 747 patients just after the procedure or after durations ranging from 30 minutes to 4 hours and in 0.1-0.2 mg and 4 µg doses. Octreotide did not prevent PEP in any of these trials. In addition, PEP was seen more frequently in the treatment group (35% vs. 11%) (84-88). In a meta-analysis of 15 randomized controlled trials, PEP was seen in 92 of 1,320 patients (7%) in the control group and in 72 of 1,301 patients (5.5%) in the treatment group. The difference was not statistically significant, and octreotide was ineffective in preventing PEP (89). In the meta-analysis of 18 randomized controlled trials, PEP was significantly lower in the group with octreotide used in high doses (>0.5 mg) than in the controls (3.4% vs. 7.5%, p=0.001), and octreotide in high doses was reported to prevent PEP (90). In another meta-analysis, octreotide was demonstrated not to decrease PEP incidence or pancreatic pain but to decrease hyperamylasemia (p=0.007) (81). In one study, octreotide was shown to decrease the severity of PEP and provide an advantage by shortening the length of hospital stay (91). Two recently conducted studies with large patient numbers reported that octreotide prevents PEP. In a multicenter randomized controlled study conducted in China, octreotide was administered in 414 patients, and 418 patients constituted the control group. PEP and hyperamylasemia were found significantly lower than in the control group

(2.42% vs. 5.6%, p=0.046, 12.32% vs. 17.42%, p=0.041, respectively) (92). In another study, octreotide was administered in high dose (500 µgx3) and for a longer duration (24 hours before ERCP); PEP was found significantly lower than in the control group (2% vs. 8.9%, p=0.03). The authors suggested prophylaxis was effective when administered at a high dose and for a long duration (93). It is clear that this approach is not cost-effective to administer in all patients.

Protease inhibitors

Prevention of trypsin activation of the intra-acinar trypsinogen and subsequent inflammatory cascade can be achieved with antiprotease agents. Aprotinin, gabexate maleate (GM), nafamostat mesylate (NM), ulinastatin, and heparin work in this manner in the prevention and treatment of acute pancreatitis.

In addition to its protease inhibition, GM has anti-inflammatory features. It has more inhibiting effects than the other circulating proteases. The first randomized controlled clinic trial was conducted in 1996, and GM was demonstrated to decrease both abdominal pain (6% vs. 14%, p=0.03) and amylase level (p=0.03) as well as PEP incidence (2% vs. 8%) compared to placebo (96). Although its efficacy was shown, the disadvantages are the cost, the need to be administered 12 hours before the procedure, and administration by IV infusion at a high dose. In a study conducted to offset these problems, the dose was limited to 500 mg and infusion duration to 6.5 hours before the procedure, with similar outcomes as 1 gram and 12-hour administrations (97). In another study, 608 patients were divided in three groups. A dose of 500 mg GM was administered to the first group 1 hour before ERCP, the same dose 1 hour after ERCP to the second group and normal saline to the third group. PEP was found as 3.9% and 3.4% in the first and second groups, respectively, significantly lower than in the placebo group (9.4%) (p<0.01). However, while necrotizing pancreatitis was seen in 1 patient from the 1st and 3rd groups, it was not seen in the 2nd group. The authors reported that since post-ERCP administration prevents PEP at the same rate as pre-ERCP administration, it would be more appropriate to identify the high-risk patients and to administer the drug on demand after ERCP (98). In a meta-analysis of six randomized controlled trials in 2000, GM significantly decreased PEP, hyperamylasemia and post-ERCP abdominal pain compared to control groups (p=0.001, p=0.007, p=0.005, respectively) (81). In the following years, a meta-analysis conducted by the same author included nine trials (82), and in a meta-analysis of four randomized controlled trials by another group (99), GM was found ineffective in the prevention of PEP, hyperamylasemia and abdominal pain.

Another protease inhibitor, ulinastatin, is used for treatment of acute pancreatitis in Japan and China. In a meta-analysis of five studies compared to placebo and two compared to GM for a total of seven randomized controlled trials, ulinastatin administered by IV route at a dose >150,000 units compared to placebo and GM decreased PEP and hyperamylasemia compared to placebo (p=0.02, p<0.001, respectively) (100). When administered just after ERCP at a low dose, ulinastatin was not found superior to placebo (101).

Nafamostat mesylate (NM) was found superior to placebo (102) and equally effective with GM in the prevention of PEP (103). In experimental models, heparin was demonstrated to inhibit pancreatic proteases, to increase microcirculation and to show an anti-inflammatory effect. In a non-randomized clinic trial (104) in 2002, PEP was significantly decreased when unfractionated heparin either at low dose (<15,000 IU/day) or high dose (15000-25000 IU/day) was administered by IV route compared to a control group (3.4% vs. 7.9%, respectively) (p=0.005). In a prospective randomized controlled trial conducted two years later by the same group, it was not found to be superior to placebo (5.42% vs. 8.8%, p=0.87).

Drugs reducing inflammation

This group includes nonsteroidal anti-inflammatory drugs (NSAID), corticosteroids, antioxidants, antibiotics, and immunomodulatory drugs. To date, the most promising outcomes in pharmacological prophylaxis have been achieved with NSAIDs. In three randomized controlled trials (106-108) with diclofenac, diclomec was administered intramuscularly in one and by rectal route as a suppository in the other two using 75-100 mg doses just after ERCP. PEP was significantly decreased compared to placebo. In a study with diclofenac used in a 50 mg dose (109), PEP incidence was similar to placebo both in the overall and high-risk patient groups (16.7% vs. 16.2%, 18% vs. 17.8%, respectively). In two studies with indomethacin (110,111), PEP and hyperamylasemia were decreased compared to placebo, but the results were not statisti-

cally significant. In two separate meta-analyses (112,113), PEP and hyperamylasemia were significantly decreased using prophylactic NSAIDs compared to placebo, and no adverse effect or mortality due to the drug was seen. NSAIDs seem to be effective in the prevention of PEP. They have the possibility for on-demand use, are easy to administer and are inexpensive. Therefore, the incidence of PEP can be decreased significantly by routine use of NSAIDs. This provides important clinical and economic benefits.

In a randomized controlled trial (114), routine antibiotic use significantly decreased PEP except in the situations where antibiotics were required (such as cholangitis, pancreatitis with complications and leukocytosis). Ceftazidime was administered as 2 grams IV 1 1/2 hours before ERCP; the PEP incidence (2.6%) was significantly decreased compared to the control group (9.4%) (p=0.009).

In a meta-analysis of seven randomized controlled trials, corticosteroids were not found superior to placebo in the prevention of PEP (12% vs. 10.8%, p=0.20) and hyperamylasemia (29.9% vs. 31.3%, p=0.6) (115).

Cytokines take an important place in the pathogenesis of acute pancreatitis. Results of immunomodulatory treatment targeting cytokines are promising (116). In a placebo-controlled trial, IL-10, an anti-inflammatory cytokine, was demonstrated to prevent PEP and to decrease hyperamylasemia independently from other risk factors with a single injection administered 30 minutes before ERCP (117). In another study, IL-10 was administered as 8 µg/kg IV injection 15 minutes before ERCP. Although PEP incidence and length of stay in the hospital decreased compared to placebo, it was not statistically significant (118). In a recent randomized, multicenter, double-blind, placebo-controlled trial of 948 patients, IL-10 was administered as 8 or 20 µg/kg and placebo as single IV injection 15–30 minutes before ERCP in patients. PEP incidence was found respectively in IL-10 (8 µg/kg), IL-10 (20 µg/kg) and placebo groups as: 15%, 22% and 14% (p=0.83 for IL-10 8 µg/kg vs placebo and 0.14 for IL-10 20 µg/kg vs placebo) (119). IL-10 was found to be superior to placebo at both doses for decreasing PEP incidence and pancreatitis severity. Immunomodulation is a subject open to research and exploration of new specific targets. Development of effective and safe drugs that can be used in humans is needed.

Oxidative stress has an important place in acute and chronic pancreatitis pathogenesis, independent of the etiology. Indicators of oxidative stress and free radical activity such as lipid peroxides have been demonstrated to increase duodenal fluid and blood flow in patients with acute and chronic pancreatitis. Antioxidant treatment can be helpful in the prevention or treatment of the inflammatory process based on these findings. Vitamin C, E, selenium, glutamine, beta-carotene, methionine, allopurinol, curcumin, precursors of glutathione, N-acetyl cysteine, and pentoxifylline are among the antioxidants used in clinical treatment (120).

Allopurinol, a xanthine oxidase inhibitor, was not found superior to placebo in the prevention of PEP and hyperamylasemia in a prospective randomized trial and two meta-analyses (121-123). Whereas in a randomized controlled trial (124), when it was given orally in high dose 3 and 15 hours before ERCP, it significantly decreased PEP (3.2% vs. 17.8%). However, in that study, sphincterectomy was performed in 43 of 125 patients with allopurinol administered and in 87 of 118 patients in the placebo group, and the difference was quite significant statistically (p<0.0001). This likely caused the low PEP incidence in the placebo group.

N-acetyl cysteine is a free radical cleaner stimulating glutathione synthesis. It was used as IV before and after ERCP in two randomized controlled trials and was not found superior to placebo in the prevention of PEP and hyperamylasemia (125,126).

Beta-carotene is a natural antioxidant. In a double-blind trial, natural beta-carotene was administered as single dose 12 hours before ERCP. PEP incidence was not different from placebo, but severe pancreatitis was seen less often, and no adverse effects were reported (127).

Platelet activating factor (PAF) is thought to play a role in acute pancreatitis pathogenesis, and recombinant PAF acetyl hydrolase (rPAF-AH) is thought decrease the severity of acute pancreatitis (128). In a randomized controlled trial to test this hypothesis, 600 patients were divided into three groups as two different doses of rPAF-AH (1 and 5 mg/kg) and the placebo group. PEP incidence was found at similar rates of 17.5%, 15.9% and 19.6%, respectively. rPAF-AH was not helpful in preventing PEP.

Finally, a sophisticated study (129) in the pharmacological prophylaxis of PEP will be mentioned. In this study of the neurogenic pathway, sensitive to pH, in PEP pathogenesis, it was demonstrated

that when contrast agents with a pH of 6.9 were injected into the pancreatic duct, edema and neutrophil infiltration and histological damage occurred in the pancreas. When the contrast agent with a pH of 7.3 was injected with the same pressure, the damage was less severe. If the pH of the contrast agent can be increased, perhaps the risk of pancreatitis can be decreased. Further clinical trials are needed to clarify this subject.

To what extent are the findings obtained from all of the studies described in this review reflected in clinical practice? In a recent survey on this subject (130), endoscopists were asked how often they placed pancreatic stents and used NSAIDs to prevent PEP. Questionnaire forms were sent to 467 endoscopists; 141 endoscopists from 29 countries responded (30%). Of the responders, 83% had not used NSAIDs because scientific evidence was not felt to be sufficient. Twenty-one percent of them had not placed a stent probably due to lack of experience. Fewer than half had attempted to place a stent. In conclusion, despite the scientific evidence, neither pancreatic stent nor NSAIDs seem to have taken a place in clinical practice in Europe.

CONCLUSION

Post-ERCP pancreatitis (PEP) is the most common complication of ERCP despite the technological developments and improved endoscopist skill levels. The most important ways to decrease PEP are proper patient selection for ERCP with appropriate indications, use of other imaging methods instead of diagnostic ERCP, especially in high-risk patients, and referral of high-risk patients to more experienced centers. Guidewire cannulation prevents PEP by decreasing trauma at the papilla of Vater. Endoscopists should gain experience in accurately predicting which accessory is most effective for biliary cannulation by the appearance of the papilla and endoscope position. Two efficient methods that can be applied on demand to prevent PEP are pancreatic stent insertion and diclofenac use. Pancreatic stent placement is not always successful, and failure after attempted placement may lead to pancreatitis. Diclofenac seems to be a unique drug and is recommended for routine use to prevent PEP as an easy-to-use, efficient, safe, and inexpensive drug.

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