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Endoscopic Retrograde Cholangiopancreatography (ERCP) Related Acute Pancreatitis

Zoltán Döbrönte
University of Pécs, Faculty of Health Sciences and Markusovszky Teaching Hospital, Department of Gastroenterology and Internal Medicine, Szombathely, Hungary

1. Introduction

Despite the significant development in endoscope technology and in availability of endoscopic accessories and the spreading of well structured ERCP training the incidence of ERCP-related acute pancreatitis has been little changed in the last three decades. One of the explanations of this contradiction may be that post-ERCP pancreatitis occurs nowadays more often in case of therapeutic intervention compared to the diagnostic ERCP and the need for solely diagnostic ERCP is rapidly declining due to the development of less invasive imaging methods such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS). ERCP has become an almost exclusive therapeutic procedure.

2. Incidence of post-ERCP pancreatitis

Endoscopic retrograde cholangiopancreatography (ERCP) has the greatest potential for complications among the gastrointestinal endoscopic procedures. The most common complication is acute pancreatitis with an overall incidence of 2-10 %, which can reach even 30 % in the presence of certain risk factors. The post-ERCP pancreatitis is most often mild, or less commonly moderate, but in about 10% of cases (about 0.4-0.6 % of the procedures performed) it is severe and potentially fatal. The mortality rate is about 0.1-0.5 %. Furthermore asymptomatic hyperamylasemia occurs in 35-70 % in patients undergoing ERCP. The wide interval of the published incidence of pancreatitis can be explained by and, depends on the criteria used for diagnosis, the type and duration of follow-up of patients involved in the studies, the levels of endoscopic expertise and, the frequency of patients-and procedure-related risk factors in the patient population (Cotton et al. 2009).

3. Definition of post-ERCP pancreatitis

A transient elevation in the serum amylase concentration without clinical signs of pancreatitis is common following ERCP and abdominal pain is also a frequent complaint due to distension caused by intestinal retention of air insufflated during the procedure. Therefore clear definition is mandatory for exact evaluation of clinical trials, for comparing
the results of different publications and for the standardised management in the prevention and treatment of ERCP related pancreatitis.

The current definition is based on an attempt at consensus in 1991 (Cotton et al.). According to this proposal post-ERCP pancreatitis was originally defined as „clinical pancreatitis with serum amylase at least three times normal at more than 24 hours after the procedure, requiring hospital admission or a prolongation of planned admission“. On the basis of this definition the widely excepted criteria for the diagnosis of post-ERCP pancreatitis are the followings: pancreatic-type abdominal pain and symptoms with onset after ERCP and severe enough to require hospital stay or to extend the length of stay of already hospitalised patients, serum amylase and/or lipase at least 3 times higher than the upper limit of normal values in 24 hours after the procedure, and/or CT/MRI consistent with the diagnosis of acute pancreatitis.

The severity of attack was graded by the above consensus report as mild, moderate and severe. A mild post-ERCP pancreatitis was defined as a need for hospital stay up to 3 days, a moderate pancreatitis was defined as a need for hospital stay for 4-10 days, and a severe pancreatitis as more than 10 days with a significant complication. The European Society of Gastrointestinal Endoscopy (ESGE) guideline recommends a more specific grading system of the severity of pancreatitis for the future (Dumonceau et al. 2010). The Atlanta classification can also be used for the estimation of severity of the post-ERCP pancreatitis, on the basis of the absence or presence of local (documented by CT) or systemic complications, independently of the duration of the hospital stay.

4. Pathophysiology of post-ERCP hyperamylasemia and pancreatitis

Pathomechanism of post-ERCP pancreatitis is of multifactorial nature, but it has not been fully understood yet. It seems to be an inflammatory response to mechanical, hydrostatic, thermal, bacterial and chemical insults that results from cannulation and other instrumentation of the papilla and injection of contrast medium into the pancreatic duct. These initiating factors may act independently or in combination.

Mechanical trauma: repeated cannulation attempts or prolonged manipulation around the papillary orifice may cause injury of the pancreatic sphincter or proximal pancreatic duct and may lead to mechanical obstruction due to oedema of the pancreatic sphincter or to prolonged spasms in patients with sphincter of Oddi hypertension.

Hydrostatic factor: pressure increase in the pancreatic duct may be related to overinjection of contrast medium (parenchymography) or to pancreatic manometry without distal aspiration. The consecutive capillary endothelial injury leads to an increase in capillary permeability. It has been suggested that this capillary injury might be mediated by oxygen-derived free radicals.

Thermal injury: electrocautery current may produce edema of the pancreatic orifice and thermal damage of the periampullary acinar cells. Coagulation or blended current causes more tissue injury than cutting current.

Infection: bacterial injury from contaminated endoscope channel or accessories may occur.

Chemical factor: injection of contrast medium into the pancreatic duct may result in chemical injury. High osmolarity contrast agents are thought to play a role in the induction of hyperamylasemia, although a meta-analysis (George et al. 2004) could not confirm it.

Enzymatic factor: intestinal content may activate intrapancreatic proteolytic enzymes. The above initiating factors lead to autodigestion due to premature intracellular activation of pancreatic proteolytic enzymes, and to release of inflammatory cytokines producing both
local and systemic effects (Demols & Deviere 2003, Karne & Gorelick 1999). The severity of pancreatitis is determined by the intensity of the inflammatory cascade and systemic response. The process itself is believed the same as for other forms of acute pancreatitis.

5. Risk factors of ERCP related pancreatitis

Stratification of patients into low or high risk categories is important pre-investigational information to take the potential benefit and risk of procedure into account, to consider patient referral to a tertiary centre, and for selection of prophylactic measures. A number of risk factors acting independently or in combination have been identified. They can be categorised as patient related, procedure related, and investigator related risk factors.

5.1 Patient related risk factors

A multivariate analysis of prospective studies found as significant patient-related risk factors the followings: young age, female gender, suspected sphincter of Oddi dysfunction, previous post-ERCP pancreatitis, recurrent acute pancreatitis, and lack of evidence of chronic pancreatitis (Freeman & Guda, 2004). The European Society of Gastrointestinal Endoscopy (ESGE) guideline further differentiates between definite and likely risk factors based on the strength of evidence from prospective studies (Dumonceau et al., 2010) (Table 1). These risk factors can act synergistically, putting patients at high risk for post-ERCP pancreatitis.

<table>
<thead>
<tr>
<th>Definite risk factors</th>
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</thead>
<tbody>
<tr>
<td>Suspected sphincter of Oddi dysfunction</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>Previous pancreatitis</td>
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</tbody>
</table>

<table>
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<tr>
<th>Likely risk factors</th>
</tr>
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<tbody>
<tr>
<td>Younger age</td>
</tr>
<tr>
<td>Non-dilated extrahepatic bile ducts</td>
</tr>
<tr>
<td>Absence of chronic pancreatitis</td>
</tr>
<tr>
<td>Normal serum bilirubin</td>
</tr>
</tbody>
</table>

Table 1. Patient-related risk factors of post-ERCP pancreatitis (Adapted from ref. Dumonceau et al., 2010)

The association of these predictors to post-ERCP pancreatitis proved to be the strongest in patients with known or suspected sphincter of Oddi dysfunction with a complication rate of 10-30%. All of the risk factors are independently important, but they may have a cumulative effect. In a prospective multicentre study (Freeman et al. 2001) the highest risk (42%) was found in the following combination of the predictors for post-ERCP pancreatitis: female patients, normal serum bilirubin level, suspected sphincter of Oddi dysfunction, and difficult bile duct cannulation. It can be postulated that a prolonged pancreatic sphincter spasm may be an important common factor in the induction of pancreatitis in the group of patients with increased risk for post-ERCP pancreatitis, and that this group of patients have a lower threshold for developing pancreatitis after ERCP.

The higher risk in younger age might depend on the lack of age-related atrophy of the pancreatic glands and on the higher prevalence of sphincter of Oddi dysfunction in young people, predominantly in females. Similarly to the aging, the protective role of chronic
pancreatitis can be explained by atrophy and decreased enzymatic activity. Patients with normal serum bilirubin and non-dilated stonefree bile ducts reported as predictors for developing post-ERCP pancreatitis may also have sphincter of Oddi dysfunction not having been taken into consideration in the diagnosis, especially regarding patients complaining also biliary pain. A history of acute pancreatitis independently of the etiology is the second most important risk factor after sphincter of Oddi dysfunction, and it should be taken into consideration before planning an ERCP.

5.2 Procedure related risk factors

Procedure-related risk factors are similarly important as patient-related factors in determining the incidence and severity of post-ERCP pancreatitis (Fig 1.). Various procedures are associated with higher risk of post-ERCP pancreatitis (Table 2.), most of them documented by multivariate analyses. For example role of papillectomy has not been analysed, but it can be considered as a definitive risk factor on the basis of prospective studies.

<table>
<thead>
<tr>
<th>Definite risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic duct cannulation and contrast injection</td>
</tr>
<tr>
<td>Multiple attempts of cannulation</td>
</tr>
<tr>
<td>Precut sphincterotomy</td>
</tr>
<tr>
<td>Endoscopic papillectomy</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Other risk factors</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Balloon dilation of the sphincter</td>
</tr>
<tr>
<td>Sphincter of Oddi manometry</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
</tr>
<tr>
<td>Pancreatic brush cytology</td>
</tr>
<tr>
<td>Failure to clear bile duct stones</td>
</tr>
<tr>
<td>Difficult or failed cannulation</td>
</tr>
</tbody>
</table>

Table 2. Procedure-related risk factors of post-ERCP pancreatitis

Repeated attempts at cannulating, also without pancreatic duct contrast injection is associated with high incidence of pancreatitis. This fact supports that papillary edema and sphincter spasm, rather than hydrostatic ductal and contrast agent injury are the major factors in the induction of post-ERCP pancreatitis. The risk rate seems to progressively increase with the number of attempts. More than 10 cannulation attempts can increase the risk of pancreatitis about 15-fold (Testoni et al. 2010). The contrast injection itself can induce pancreatitis due to hydrostatic injury from pancreatic duct overfilling, which is the most pronounced in cases of parenchymography. The use of lower ionic contrast agents does not result in lower frequency of pancreatitis than that of the conventional ones.

Pre-cut sphincterotomy is associated with a threefold increase of post-procedure pancreatitis, however the risk is likely mainly investigator dependent and seems to be lower in experts hands. Moreover, early pre-cut may be safer than delayed pre-cut performed after multiple cannulation attempts. The overall risk of pancreatitis after pre-cut sphincterotomy is less than after repeated attempts at standard cannulation. Out of the two techniques of needle knife precut, fistulotomy where the precut is separate from the papillary orifice, seems to be accompanied with less pancreatitis than precut starting at the papillary orifice.
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(Mavrodiannis et al. 1999), although high level evidence fails to support the preference of fistulotomy.

Fig. 1. Endoscopic retrograde cholangiopancreatogram of a young woman with gallbladder stones. Non-dilated bile ducts, young age, and female gender represent patient related risk factors, and contrast injection into the pancreatic duct a procedure related risk factor for post-ERCP pancreatitis.

Pancreatitis occurs after endoscopic papillectomy performed like a snare polypectomy using a side-viewing duodenoscope in 15-20 %. Therefore papillectomy (ampullectomy) should perform only by well-trained and experienced endoscopists. The incidence and severity of this complication can be significantly reduced by prophylactic pancreatic duct stenting (Wong, 2004). Pancreatitis caused by stenosis of the pancreatic duct orifice can also be a late complication after papillectomy (Norton et al., 2002).

Biliary sphincterotomy itself is not associated with an increased risk of pancreatitis. Currently the use of pure cut current is advisable, because it causes less tissue injury and edema than coagulation current. On the contrary to biliary sphincterotomy balloon dilatation of the intact biliary sphincter has been associated with a high incidence of pancreatitis, therefore its use is not advisable in the presence of patient-related risk factors, especially in patients with sphincter of Oddi hypertension. Large diameter biliary stent without sphincterotomy can also induce pancreatitis due to compression of the pancreatic sphincter (Tarnasky et al., 1997). On the contrary, biliary-stent exchange in sphincterotomised patients causes less-frequent pancreatitis compared to other ERCP procedures (Cotton et al. 2008).

Sphincter of Oddi manometry using standard perfusion catheter is associated with a substantial incidence of pancreatitis. The risk can be significantly reduced by using modified triple lumen catheter with simultaneous aspiration or by using a microtransducer catheter. In two randomised controlled studies the incidence of post-ERCP pancreatitis was found using the alternative catheters in comparison with the standard perfusion catheter 3.0% vs. 23.5 % and 3.1% vs. 13.8 % (Sherman et al. 1990, Wehrmann et al. 2003).
Pancreatic sphincterotomy was associated with high risk of pancreatitis in a recent prospective multicentre study only in univariate analysis (Testoni et al., 2010), in agreement with some earlier reports (Freeman et al., 2001, Cheng et al. 2006). As independent risk factor proved to be only minor papilla sphincterotomy.

What other procedure risk factors concern, pancreatic brush cytology can cause pancreatitis due to edema in consequence of mechanical trauma of the pancreatic duct. In case of failure to clear the bile duct during ERCP residual stones can induce biliary pancreatitis.

5.3 Investigator related risk factors
Data about a potential relationship between post-ERCP pancreatitis incidence and endoscopist's experience in the technique defined as annual case volume (the median number of ERCPs per endoscopists/year) are conflicting. Endoscopist's inexperience and trainee participation may be associated with a higher incidence as it was shown in some of the studies, while others could not confirm it. This might be explained by the fact that in high-volume centres there are more patients with high risk for potential post-ERCP pancreatitis and larger number of procedures at higher degree of difficulty.

6. Prophylaxis of ERCP related pancreatitis
6.1. Mechanical techniques
6.1.1 Pancreatic stent placement
The purpose of placing a temporary pancreatic duct stent is to sustain the pancreatic outflow in the face of relative obstruction due to edema and sphincter of Oddi spasm caused by manipulations of the papilla. A meta-analysis of eight randomized controlled trials demonstrated that short term pancreatic stent placement reduces the incidence of post-ERCP pancreatitis (Mazaki et al 2010) (Fig. 2.). Sofuni et al (2007) found significant benefit of stent placement only in patients at high risk for pancreatitis, and it seems to be not cost-effective in patients at average risk (Das A et al. 2007). Therefore, the use of prophylactic pancreatic stenting is generally proposed only for patients who are at high risk for developing pancreatitis after ERCP. Similar standpoint is represented also in the recommendation of the ESGE guideline (Dumonceau et al. 2010).

Fig. 2. The effect of pancreatic stent placement on the incidence of post-ERCP pancreatitis according to meta-analysis (Mazaki et al. 2010)
What kind of plastic stent should be used? 3 mm long 3-5 Fr straight polyethylene plastic stents without internal flanges (for promoting of spontaneous elimination in few days following the insertion) and with one or two external flanges (for preventing proximal migration) are recommended for prophylactic purpose (Fig. 3). Stents of 3-Fr and 5-Fr in diameter proved to be similarly effective, but the insertion of 5-Fr stents seems to be easier and faster (Zolotarevsky et al. 2011).

Fig. 3. Pancreatic stent without internal flanges
The stent migrates spontaneously into the duodenum within two weeks in most of the cases. Within 5 to 10 days after the stent insertion an X-ray control and, when the stent is in place yet, endoscopic stent removal is recommended because of the risk of stent-induced damage to the pancreatic duct. Adverse events including pancreatitis following stenting of the main pancreatic duct occur in 4.2-4.6 %, but the incidence of pancreatitis after failed cannulation attempts may reach even 65 % (Freeman et al. 2004). Therefore this is a technique for experienced endoscopist.

6.1.2 Pancreatic guide wire placement for facilitation of bile duct cannulation
Data about the effectiveness of pancreatic guide wire placement in the prevention of post-ERCP pancreatitis are still controversial. In patients with difficult bile duct cannulation successful biliary cannulation can be achieved by pancreatic guide wire-assisted technique in more than 70% of the cases (Dumonceau et al. 2010). If this method is used, a pancreatic stent should be placed for prophylaxis of pancreatitis (Fig 4.). For the same reason pancreatic stenting can be useful also in cases in which biliary cannulation remains unsuccessful.

6.1.3 Guide wire-assisted deep biliary cannulation
Insertion of 0.035-inch diameter guide-wire into the papilla directly or advancing the guide-wire through the sphincterotome inserted into the papilla for deep biliary cannulation reduces the risk of post-ERCP pancreatitis due to promotion of selective primary cannulation. This method may namely diminish traumatic injury to the pancreatic duct and hydrostatic pressure increase associated with injection of contrast material. Therefore, the guide wire-assisted technique is advised for deep biliary cannulation by the ESGE guideline (Dumonceau et al. 2010). However, in a prospective randomised trial this technique was associated with a lower rate of post-ERCP pancreatitis only with the exception of cases where the technique was performed in patients with sphincter of Oddi dysfunction or where unintentional pancreas guide wire cannulation occurred (Lee et al 2009).
6.2 Pharmacological agents
Several agents have been tested experimentally and in clinical trials for potential efficacy in the prevention of ERCP induced pancreatitis. Chemoprevention studies have targeted the following mechanism of action: reduction of pancreatic secretion, prevention of intra-acinar trypsinogen activation, interruption of inflammatory cascade, relaxation of sphincter of Oddi, and prevention of infection. The majority of the investigated pharmacological agents appeared promising in initial randomised single-centre clinical studies however, conflicting results were obtained from larger multi-centre trials (Table 3.).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>Somatostatin</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Gabexate mesilate</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Ulanistatin</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Nifedipin</td>
<td>No</td>
</tr>
<tr>
<td>Lidocain spray</td>
<td>No</td>
</tr>
<tr>
<td>Epinephrine spray</td>
<td>No</td>
</tr>
<tr>
<td>Botulinum toxin intrapapillary</td>
<td>Need for more trials</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>No</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>No</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>No</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>No</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>No</td>
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<tr>
<td>Semapimod</td>
<td>No</td>
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<tr>
<td>Acethylhydrolase</td>
<td>No</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Yes, but need for more trials</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Yes, but need for more trials</td>
</tr>
</tbody>
</table>

Table 3. Medications tested for prophylaxis of post-ERCP pancreatitis

Fig. 4. A case of difficult bile duct cannulation. Following pancreatic guide wire-assisted technique pancreatic stent was placed for prevention of post-ERCP pancreatitis
6.2.1 Reduction of pancreatic enzyme secretion
Somatostatin and its long-acting analogue octreotide affect the exocrine function of the pancreas directly by reducing the secretion of digestive enzymes and indirectly by inhibiting the production of secretin and cholecystokinin. According to a meta-analysis pooling the data from ten high-quality randomised controlled trials it can be concluded, that somatostatin did not influence the overall incidence of post-ERCP pancreatitis (Dumonceau et al. 2010). Although a significant risk reduction of post-ERCP pancreatitis was found in four randomised controlled trial, when somatostatin was administered in continuous infusion for longer than 12 hours, and in two studies, when somatostatin was given as a single bolus, the question is yet open, weather using specific dose-schedules somatostatin might be more efficacious (Arvanatidis et al. 2004).

Concerning the long-acting somatostatin analogue octreotide the same conclusion can be drawn based on an ad hoc meta-analysis of eight randomised controlled trials (Dumonceau et al. 2010). Octreotide can reduce the ERCP-induced hyperamylasemia, but this effect can only be shown, if endoscopic sphincterotomy is simultaneously performed (Tulassay et al. 1997). Octreotide increases namely the tone of the sphincter of Oddi, and therefore this partial beneficial effect of the reduced enzyme secretion may be effective only with sphincterotomy together. Some data suggest that the effect of octreotide may be dose-dependent and more than 0.5 mg of octreotide may be beneficial (Zhang Y et al. 2009), but it should yet be clarified in future studies.

6.2.2 Protease inhibitors
Antiprotease agents were tested for prophylaxis of post-ERCP pancreatitis with the purpose of prevention of intra-acinar trypsinogen activation to trypsin and that of the subsequent inflammatory cascade. Gabexate mesilate in six randomised controlled trials, while ulanistatin in four randomised controlled trials have been evaluated. Furthermore, the prophylactic effect of gabexate with ulanistatin was compared in two clinical trials. The results can be summarised by stating that, although there is a small risk reduction, particularly in the ulanistatin subgroup, there is no solid evidence that antiprotease drugs significantly influence the incidence of post-ERCP pancreatitis. The same conclusion can be drawn from a recently published meta-analysis (Seta & Noguchi 2011) on the basis of which it can be stated that the primary studies were not of high quality enough to come to the proper consequences. Nevertheless, protease inhibitors are costly.

6.2.3 Sphincter relaxants
Nitroglycerin (glycerine trinitrate) proved to be effective in some reports, but ineffective in others. Based on two meta-analyses (Bang et al. 2009, Shao et al. 2010) of pooled data from five randomised controlled trials it can be concluded that nitroglycerin administered orally or sublingual may reduce the incidence of post-ERCP pancreatitis, but transdermal nitroglycerin is ineffective. The use of nitroglycerin is often associated with transient hypotension and headache, therefore the ESGE guideline does not recommend its routine use in the prophylaxis of post-ERCP pancreatitis (Dumonceau et al. 2010). Nifedipin was also tested, because calcium channel blockers have proved to be effective in the prevention of experimental pancreatitis. In clinical trials, however, nifedipin failed to show a significant effect in the prevention of post-ERCP pancreatitis (Prat et al. 2002).
Other drugs (lidocaine spray, epinephrine spray, Botulinum toxin injected intrapapillary) tested with the intention of reducing the sphincter of Oddi pressure failed to show any efficacy (Gorelick et al. 2004, Matsushita et al. 2009, Schwartz et al. 2004).

6.2.4 Antibiotics
There is only a single study evaluating the ceftazidime for prophylaxis of post-ERCP pancreatitis. This antibiotic was given in a dose of 2 g intravenously 30 min prior to the investigation and a significant reduction in the incidence of post-ERCP pancreatitis was observed (Raty et al. 2001). Further data are necessary to establish the real place of antibiotics in the prevention of ERCP-related pancreatitis.

6.2.5 Antioxidants
The following antioxidant agents were investigated for prevention of ERCP related pancreatitis: N-acetylcysteine (Katsinelos P. et al. 2005), beta-carotene (Lavy et al. 2004) and allopurinol. The free radical scavenger N-acetylcysteine and beta-carotene failed to show any beneficial effect. Allopurinol is a xanthine oxidase inhibitor and an antioxidant with antiapoptotic property. Four randomised clinical trials dealing with its effect in the prevention of post-ERCP hyperamylasemia and pancreatitis were published. Three of them reported negative outcomes but in two studies allopurinol proved to be effective in the reduction of the incidence of hyperamylasemia, and in one of them also in that of acute pancreatitis, particularly in patients submitted to high risk procedures (Martinez-Torres et al. 2009). Allopurinol was administered orally in a dose of 300 mg at 15 and 3 hours before ERCP.

6.2.6 Antiinflammatory drugs
Several agents acting by interruption of the inflammatory cascade were tested. Glucocorticoids do not reduce the incidence of post-ERCP pancreatitis according to a meta-analysis based on six randomised controlled trials (Bay et al. 2008). Similarly to glucocorticoids pentoxifylline, semapimod, and acethylhydrolase (a recombinant platelet-activating factor) all proved to be ineffective. Interleukin-10 reduced the incidence and severity of post-ERCP pancreatitis in an initial study (Deviere et al. 2001), but further trials could not confirm its effectiveness. As suggested by observational and animal studies, heparin has also an anti-inflammatory effect, inhibit the activity of pancreatic proteases and improves pancreatic circulation, but in clinical randomised controlled trials neither unfractionated heparin (Barkay et al. 2008), nor low molecular-weight heparin (Rabenstein T et al 2004) proved to be effective in the prophylaxis of post-ERCP pancreatitis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit phospholipase A2 which has an early role in the inflammatory cascade in acute pancreatitis. Inhibition of phospholipase A2 results in suppression of several important classes of proinflammatory lipids (prostaglandins, leukotriens, platelet-activating factor). Furthermore, NSAIDs inhibit neutrophyl-endothelial cell attachment. Indomethacin followed by diclofenac is the most potent NSAID with regard to phospholipase A2 inhibition. Indomethacin has shown to decrease the mortality of experimental pancreatitis in animals (Wildenhain et al 1989). Four prospective randomised controlled clinical studies have been published until now that compared rectally administered indomethacin or diclofenac vs. placebo (Murray et al. 2003, Sotoudehmanesh R et al. 2007, Montano Loza et al. 2007, Koshbaten M et al. 2008) (Fig. 5.).
On the basis of three meta-analyses using the data of these studies rectally administered indomethacin and diclofenac in a dose of 100 mg proved to be effective in the decrease of incidence of post-ERCP pancreatitis (Elmunser et al. 2008, Zheng et al. 2008, Dai et al. 2009).

The reduction seems to be similar regardless of the degree of the risk (Zheng et al. 2008). Limitation of the original studies is the small number of the trials performed only in three countries. Therefore some scepticism related to the clinical efficacy of NSAIDs in the prophylaxis of post-ERCP pancreatitis exists, all the more because several agents tested before have shown promise in early single-centre studies, but the results were disappointing in larger multicentre randomised controlled trials. Furthermore it has to be mentioned that diclofenac administered intramuscularly or orally did not proved to be effective in lowering the rate of post-ERCP pancreatitis significantly (Cheon et al. 2007, Senol et al 2009). Further multicentre controlled studies are awaited for confirmation of the promising results of the foregoing trials. Nevertheless NSAIDs in a single dose are relatively safe, cheap, and easy to use. Therefore 100 mg of indomethacin or diclofenac administered rectally immediately before or after ERCP is routinely recommended. This standpoint is reflected also in the ESGE guidelines (Dumonceau et al. 2010).

6.3 Post-procedure management (Follow-up after ERCP)

Post-ERCP pancreatitis is an unforeseen complication but it can be predicted by measuring the serum amylase concentration at 2-4 hours after the procedure. It should be taken into account, however, that hyperamylasemia without pancreatitis following ERCP is well recognised and abdominal discomfort for some hours after ERCP due to intestinal distension by air insufflated during the investigation is a commonly occurring symptom, in particular in patients with functional gastrointestinal dysfunction. It is advisable to restrict oral intake of water for four hours and until serum amylase value is available. Serum amylase concentration less than 1.5 times the upper limit of normal value almost excludes post-ERCP pancreatitis and the patient can be discharged on the day of ERCP. For patients with four hours serum amylase levels more than twice the upper limit, with ongoing

(RCT: randomised controlled trial)

Fig. 5. Incidence of post-ERCP pancreatitis: rectally administered NSAIDs versus placebo.

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abdominal pain / tenderness or fever, fasting and parenteral fluid replacement is recommended. The same policy is advised in the presence of any risk factor of post-procedural pancreatitis at least for 24 hour after ERCP. Further management is depending on the 24 hour serum amylase level and clinical signs of pancreatitis.

6.4 Principles of prevention and reduction of severity of ERCP-induced pancreatitis

Following factors listed below should be considered when indicating and performing ERCP.

1. Because post-ERCP pancreatitis can be severe, life-threatening or even fatal, careful and adequate patient selection is one of the most important and the most effective preventive measures. ERCP should not be performed when the indication is not clear or the procedure is unlikely to benefit the patient. In borderline indications and when the aim of ERCP is solely diagnostic, non-invasive imaging methods, magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound should be performed first. Endoscopists should always take a risk-benefit analysis with knowledge of the identified patient related risk factors, when deciding whether to perform an ERCP.

2. Referral of patients at high risk for post-ERCP pancreatitis to a great volume specialist centre should be considered.

3. Minimal use of contrast material, avoidance of repeated attempts of pancreatic cannulation and use of guide wire to gain access or use of dual wire technique can be effective measures for prophylaxis in certain cases.

4. Risk related ERCP techniques should be avoided when possible.

5. Pharmacological prophylaxis with periprocedural rectal administration of NSAIDs (indomethacin or diclofenac) as a cheap, practical and safe method is routinely recommended.

6. Prophylactic placement of short 5 Fr pancreatic stent without inner flanges should be strongly considered for patients at high risk for development of post-ERCP pancreatitis.

7. Early screening for post-ERCP pancreatitis following the procedure and appropriate management is also important for the prevention or for reduction of the severity of ERCP-related pancreatitis.

The recommendations above are in concordance with the European Society of Gastrointestinal Endoscopy guideline (Dumonceau et al., 2010).

7. Therapy of post-ERCP pancreatitis

The treatment of ERCP related pancreatitis is the same as that of the acute pancreatitis of other etiologies and it depends considerably on the severity of the pancreatitis. The therapy is mainly supportive including fasting, adequate correction of hypovolemia, and maintenance of optimal fluid balance, close monitoring for signs of local and systemic complications, and adequate pain control. Patients with mild pancreatitis can generally begin oral food intake in few days. The outflow of the pancreatic juice can be tried to improve with spasmolytics, nitroglycerin or theophyllin. Morphine should be avoided because this drug may produce high outflow resistance due to sphincter of Oddi spasm, but pethidine / meperidine are allowed if the patient requires it for pain relief. If the efficacy of pethidine / meperidine is insufficient, epidural anesthesia is the best choice or fentanyl can be given. In cases of severe pancreatitis early nasojejunal feeding can be crucial for the maintenance of integrity of the gut mucosal barrier, hereby preventing bacterial translocation into the systemic circulation. Translocated pathogen intestinal flora is namely
one of the main sources of septic complications. Enteral feeding with appropriate energy intake has also a role in the correction of the nutritional imbalance due to the prolonged hypermetabolic state in severe acute pancreatitis. Adequate intravenous substitution is also very important, likewise early antibiotic prophylaxis in necrotizing pancreatitis - although still controversial, and effective antimicrobial treatment of the inflammatory complications. Infected pancreatic necrosis and infected pancreatic and peripancreatic fluid collections should be treated by surgery or by endoscopic or CT guided intervention. Treatment of the systemic complications has to be managed in an intensive care unit with close monitoring of the vital functions.

8. Conclusion

Acute pancreatitis is the most common and feared complication of ERCP. Post-ERCP pancreatitis is severe and potentially fatal in a significant proportion. The incidence rate has been little changed over the last decades despite important advances in endoscope and in accessory technology.

The widely accepted criteria for the diagnosis of post-ERCP pancreatitis are serum amylase and/or lipase at least 3 times higher than the upper limit of normal values in 24 hours after the procedure accompanied by new pancreatic-type abdominal pain and symptoms and severe enough to require hospital stay or to extend the length of stay of already hospitalised patients, and/or CT/MRI consistent with the diagnosis of acute pancreatitis.

The pathomechanism is not fully understood. It seems to be an inflammatory response to mechanical, hydrostatic, enzymatic, thermal, microbiological, and probably chemical insults that results from cannulation attempts and contrast material injection into the pancreatic duct.

A number of risk factors for developing pancreatitis after ERCP are known, they can categorised as patient related, procedure related, and investigator related risk factors. It is essential to identify patients at high risk to avoid unnecessary procedures or adopt protective technical or pharmacological measures. If patient related risk factors are present, first of all it is advised to consider patient’s referral to a specialist centre, or for selection of prophylactic measures. In borderline indications non-invasive imaging methods should be preferred. Out of procedure related risk factors papillary edema and sphincter spasm are the major factors in the induction of post-ERCP pancreatitis. For minimizing the risk of pancreatitis during the procedure the following measures should be kept in mind: atraumatic manipulation of the papilla, avoidance of repeated pancreatic duct cannulation and contrast injection, avoidance of balloon catheter dilatation of the intact sphincter, limited use of precut sphincterotomy and pancreatic sphincterotomy, avoiding placement of biliary stent through intact papilla, using soft-tipped guide wire to access bile duct, and using pure cut electrosurgical current.

Despite selecting patients and using protective technical measures post-ERCP pancreatitis can occur unexpectedly. Therefore prophylactic pharmacological intervention is routinely advised by means of rectal indomethacine or diclofenac immediately before or after the procedure. The administration of indomethacine and diclofenac in a single dose is safe, cheap, and easy and based on the few randomised controlled trials it seems to be effective in the decrease of the incidence of post-ERCP pancreatitis. Further randomised controlled trials are needed to prove the real efficacy of NSAIDs in the reduction of severe ERCP related
pancreatitis. For high-risk ERCPs prophylactic placement of short pancreatic stent proved to be beneficial in experienced hands, therefore its use is recommended for few days in these cases. Careful follow up, early screening for pancreatitis and appropriate management of the complication are crucial for the outcome. The treatment of post-ERCP pancreatitis itself does not differ from that of the acute pancreatitis of whatever etiology.

9. References


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Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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