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Post ERCP Pancreatitis: A Endoscopist's Night Mare! An Insight with Literature Review

Abstract

Post ERCP pancreatitis is a serious complication that, at the minimum, prolongs hospital stay and, in rare cases, causes serious morbidity and death. The potential for risk reduction has therefore been the matter of extensive research. Rectal Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) were found to be appropriate for clinical use. Pancreatic Duct (PD) stent placement is currently considered the standard of care in high-risk cases where PD entered by guide wire multiple time and contrast injection in to PD. Failure attempt at PD stenting is disastrous. In cases of pancreatic branch duct injuries caused by the PGW combination of PD stenting and rectal NSAIDs should b used because PD stenting alone may not be effective. Sublingual nitroglycerin and bolus-administered somatostatin were found to be promising agents for whom confirmatory research is needed. Additional research required to justify use to prevention of PEP for topical epinephrine, aggressive intravenous fluids and ulinastatin.

Keywords: Diclofenac; Cannulation; Stenting; Cholangitis; Epinephrine; Somatostatin; Nitroglycerin; Ulinastatin

Review Article

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Abbreviations: NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PD: Pancreatic Duct; ERCP: Endoscopic Retrograde Cholangiopancreatography; PEP: Post-ERCP Pancreatitis; ULN: Upper Limit of Normal; MRCP: Magnetic Resonance Cholangiopancreatography; EUS: Endoscopic Ultrasonography; CBD: Common Bile Duct; SO: Sphincter of Oddi; PGW: Pancreatic Guide Wire; GWs: Guide Wires

Introduction

Post-ERCP Pancreatitis (PEP) is the most common complication of Endoscopic Retrograde Cholangiopancreatography (ERCP) resulting from mechanical injury by guide wire, papillary trauma from prolonged papillary manipulation, hydrostatic & chemical injury from contrast, enzymatic injury through activation of proteolytic enzyme, infection from contaminated scope/accessory and thermal injury. PEP is a worst night mare on the following day of ERCP. It has signifiant médical, social and economic bourden on patient and liability implications on endoscopist. 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 at 24 hours of ERCP. PEP can be mild, moderate, or severe according to requirement of admission or prolongation of planned admission. Prolongation of planned admission to two to three days occurs in mild PEP, three to ten days in moderate and more than ten days in severe PEP.

Although PEP is reported to occur in 1-40% of cases, in prospective studies, it is reported to occur in 5-10% with 1% severe and 0.1% fatal cases [1]. Serum amylase values less than 1.5 times the upper limit of normal (ULN), obtained at 2-4 hours post-ERCP, almost exclude PEP and value more than 3 or 5 times the ULN at 4-6 hours post ERCP have increasing positive predictive values for PEP [2].

Patient-related risk factors for post ERCP pancreatitis

Risk of post-ERCP pancreatitis is determined not only by the characteristics of the patient but also by endoscopic techniques or maneuvers. Patient-related risk factors include younger age, suspected sphincter of Oddi dysfunction, history of previous PEP, and absence of elevated serum bilirubin [3,4]. Pancreatic contrast injection independently associated with pancreatitis risk, and risk increases with number of injections [3]. It rapidly acinarized in pancreas, hence can't be retrieved back so it remain significant risk factor for PEP. Pancreatic sphincterotomy was found to be a risk factor for pancreatitis due to thermal injury but the risk of severe pancreatitis significantly reduced if pancreatic drainage done efficiently via a pancreatic stent. Pre cut papillotomy or accessotomy to gain access to the common bile duct has uniformly been associated with a higher risk of pancreatitis [3,4]. This elevated risk emerges even after adjusting for difficulty of cannulation or early pre cut decreases PEP remain a matter of Debate.

Balloon-dilation of the biliary sphincter is an alternative to sphincterotomy for the extraction of bile duct stones. It is associated with higher risk of PEP, although two randomized trials have shown complications to be equivalent to or less than for sphincterotomy [5,6]. Sphincterotomy prior balloon sphincteroplasty may reduce risk of PEP due tearing rather than stretching of sphincter. EPBD with a guide wire left in the

pancreatic duct is useful method allowing reliable pancreatic stenting and may contribute to the prevention of pancreatitis [7].

Prevention of PEP

Patient selection and general measures

In patients with abdominal pain who have a low probability of bile duct stones, especially young women, alternative non invasive or less invasive imaging studies include Magnetic Resonance Cholangiopancreatography (MRCP) and Endoscopic Ultrasonography (EUS) should be adopted. Young female patients, with suspected SOD and a normal Common Bile Duct (CBD) and normal serum bilirubin levels are at 10 times greater risk for PEP and these patients should be properly informed about their risk. Use of Properly disinfected endoscopes & sterilized accessories, selective CBD cannulation without undue trauma to the papilla and avoidance of contrast injection into the pancreatic duct should be adopted to prevent PEP. 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 [8].

Pharmacologic agents available for PEP prophylaxis

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs are potent inhibitors of cyclooxygenase, prevent neutrophil-endothelial interactions, hamper pathogenesis of acute pancreatitis following ERCP and hence reduce the incidence of PEP. Effective PEP prophylaxis has been demonstrated using 100mg of diclofenac or indomethacin rectal suppositories. Elmunzer et al. [9] showed a clear benefit of using rectal NSAIDs to prevent PEP in high-risk individuals [9]. After long search for the "holy grail" to prevent PEP, only rectal NSAIDs seem to have emerged as feasible, because rectal NSAIDs are inexpensive with little chance of causing clinically relevant side effects; the benefit of occasionally preventing PEP outweighs the minimal risk. The European Society for Gastrointestinal Endoscopy guidelines recently recommended giving rectal indomethacin to prevent PEP in all patients undergoing ERCP [10].

In contrast prophylactic rectal indomethacin has not been found to effective in reducing the incidence or severity of PEP in consecutive patients undergoing ERCP in a recent randomised controlled trial by Levenick et al. [11] which throws some water on the fire. American Endoscopy Society guidelines don't specifically recommend using rectal NSAIDs to prevent PEP in all patients [12]. Question still exist regarding consistent effect across the spectrum of patients' risk of PEP. Optimal timing of administration recently investigated for prevention of PEP in an intention to treat analysis [13], which favours pre-procedural administration of rectal indomethacin. Recently High patient body weight was associated with a reduced effect of 100 mg diclofenac for prophylaxis of PEP [14].

Ulinastatin: It shows to be of value on preventing post-ERCP pancreatitis and hyperamylasemia for patients in average risk, when given intravenously at a dose of not less than 150,000 U, just before ERCP. In two higher quality but underpowered multicenter RCTs it was compared with placebo [15,16]. In one RCT [15], the incidence of PEP was significantly lower with ulinastatin (150,000 U administered prior to ERCP) compared with placebo. However, this benefit was not confirmed in another RCT [16]. Use of ulinastatin-containing contrast medium, instead of normal contrast has been recently demonstrated to decrease the incidence but could not completely prevent the development of post-ERCP pancreatitis.

Nitroglycerin: It is a smooth muscle relaxant that may lower sphincter of Oddi (SO) pressure and increase pancreatic parenchymal blood flow. Incidence of PEP significant reduced by nitroglycerin in two meta-analyses [17,18].

Somatostatin: It is a potent inhibitor of pancreatic exocrine function and may therefore prevent or mitigate the patho physiological processes that lead to pancreatic inflammation. Benefit has been demonstrated more consistently with bolus administration than with infusion in a meta analysis [19]. In addition, an RCT of somatostatin in combination with diclofenac demonstrated benefit.

Aggressive intravenous fluid resuscitation with lactated ringer's solution: It may be an effective intervention for PEP by favourably affecting physiologic pH. It may be more beneficial than Normal Saline as it reduces the risk of hyperchloremic acidosis. Experimental studies show that zymogens may be activated by low pH. Furthermore, low pH may also adversely impact acinar cells and make them more vulnerable to injury, thereby contributing to the increase in severity of AP. Aggressive hydration with lactated Ringer's solution (3ml/kg/h during ERCP, followed by a 20ml/kg bolus and 3ml/kg/h for 8hr after the procedure) may effectively prevent post ERCP pancreatitis as well as hyperamylasemia and pancreatic pain in patients with average risk [20].

Epinephrine: It is sprayed directly on the papilla during ERCP has been postulated to prevent PEP through direct relaxation of the Sphincter of Oddi and reduction of papillary edema by decreasing capillary permeability. On the basis of available data, topical epinephrine is not appropriate for clinical use a large-scale methodologically rigorous RCT in an appropriate patient population may be needed.

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. Difficult cannulation is generally considered as failure of biliary cannulation within 10 minutes or >10-15 attempts at cannulation. Early use of pre-cut sphincterotomy, wire-guided biliary cannulation, pancreatic guide wire (PGW) biliary cannulation that facilitate the cannulation can reduce PEP [21].

Pre-cut biliary sphincterotomy: It is used for difficult biliary cannulation and 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 or early use of pre-cut sphincterotomy actually decrease risk of PEP because of less trauma by less attempt at failed biliary cannulation. In a study, female gender, partial pancreatic drainage and more than 10 attempts to cannulate the papilla were identified as independent risk factors for PEP, but were pre-cut biliary sphincterotomy not found to be a risk factor [22].

Wire-guided biliary cannulation: It increases the success rate of primary cannulation without undue papillary trauma and pancreatic contrast injection. Hence, it significantly decreases the risk of PEP compared to standard cannulation techniques using contrast alone which is obsolete now [23,24].

Pancreatic Guide Wire (PGW) placement: This technique is a new technique to gain access to the bile duct and to reduce the risk of PEP after failure of traditional techniques. The technique involves inserting a first guide wire deep into the PD. A second guide wire is then used to probe the papilla to gain access to the bile duct in 11' O clock direction. The first guide wire facilitates access to the bile duct by blocking the PD opening. PGW should always followed by pancreatic stent placement. One concern about PGW, especially in cases involving tortuous pancreatic ducts when guide wire resistance arises during PGW placement, injection of minimal dose of contrast medium into the pancreatic duct in order to adjust the direction of the GW may be helpful to prevent pancreatic duct injury due to accidental guide wire insertion into a pancreatic side branch duct.

Short-length guide wires (GWs): These are controlled by the endoscopist shorten procedural time, decrease trauma at the papilla and reduce PEP. In a prospective randomized trial [25], using short GWs, the mean exchange time was significantly reduced in the short GW group compared to long GW group.

Role of stenting for prevention of post ERCP pancreatitis: Several studies have recently shown that deep pancreatic guide wire passage alone (independent of contrast medium injection), especially if repeated, is in fact a major risk for post-ERCP pancreatitis unless it is followed by a pancreatic stent. Although the mere avoidance of PD manipulation or injection might seem appealing, it is often possible. Placement of trans sphincteric pancreatic stents is a relatively new and increasingly adopted approach to reduce the risk of post ERCP pancreatitis. The mechanism by which they work is not clearly understood. In theory, stents serve to preserve flow of pancreatic juice after pancreatic sphincter instrumentation and/or to empty the gland of reactive enzyme substrate. According to this "plumbing" concept, drainage of manipulated pancreatic ducts prevents pancreatitis just as drainage of obstructed bile ducts prevents cholangitis.

The evidence that pancreatic stent placement reduces rates of PEP in high risk patients is substantial.

A meta-analysis of five prospective studies showed that risk of PEP without stents was three-fold higher than for with pancreatic stents (15.5% vs. 5.8%) [26]. The major limitation of the available studies is a lack of analysis by intention-to-treat, in that patients with failed pancreatic stent placement were excluded, a group in whom pancreatitis rates have been found to be high.

Caveats of pancreatic stenting as a strategy to prevent post-ERCP pancreatitis are substantial. A recent study [27] confirmed that failed attempted pancreatic stent placement was very risky; with two-thirds of patients developing moderate or severe pancreatitis implying that pancreatic stent placement should only be considered when it can almost certainly be followed to completion. If PEP occurs due to pancreatic branch duct injuries caused by the PGW, pancreatic stenting will not be useful for preventing PEP.

Conclusion

So, the best hope for prevention of PEP lies in careful selection of patients for ERCP, with avoidance of unnecessary or marginally indicated cases. General measures for prevention of PEP includes proper training of endoscopist and maintaining proficiency, adequate disinfection, avoidance of diagnostic ERCP, avoidance of repeated cannulation and injection of PD, careful use of electrocautery and avoidance of balloon dilation especially higher-risk patients such as younger patients who are anicteric.

Two efficient specific 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. As per my personal experience for PEP, other than routine use of diclofenac suppository PD stenting always useful after repeated PD wire cannulation and double guide wire CBD cannulation and epinephrine spray at ampulla after prolonged papillary manipulation helped me a lot for preventing PEP.

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