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REVIEW

Preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: What can be done?

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Abstract

Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is the most common complication of endoscopic retrograde cholangiopancreatography. The incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis varies substantially and is reported around 1%-10%, although there are some reports with an incidence of around 30%. Usually, PEP is a mild or moderate pancreatitis, but in some instances it can be severe and fatal. Generally, it is defined as the onset of new pancreatic-type abdominal pain severe enough to require hospital admission or prolonged hospital stay with levels of serum amylase two to three times greater than normal, occurring 24 h after ERCP. Several methods have been adopted for preventing pancreatitis, such as pharmacological or endoscopic approaches. Regarding medical prevention, only non-steroidal anti-inflammatory drugs, namely diclofenac sodium and indomethacin, are recommended, but there are some other drugs which have some potential benefits in reducing the incidence of post-ERCP pancreatitis. Endoscopic preventive measures include cannulation (wire guided) and pancreatic stenting, while the adoption of the early pre-cut technique is still arguable. This review will attempt to present and discuss different ways of preventing post-ERCP pancreatitis.

Key words: Endoscopic retrograde cholangiopancreatography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Sphincterotomy

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP) is a widely used procedure for diagnosing and treating diseases of the pancreatobiliary tree. Post-ERCP pancreatitis is the most frequent complication. Prophylactic measures of post-endoscopic pancreatitis include pharmacological and mechanical ERCP related approaches. Prevention is suboptimal and still not widely accepted.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a widely used procedure for diagnosing and treating diseases of the pancreatobiliary tree, with over 500000 ERCP procedures performed annually in the United States alone[1]. Most common complications of ERCP are hemorrhage, pancreatitis, cholangitis and perforation, with pancreatitis after ERCP, or post-endoscopic pancreatitis (PEP) being the most frequent complication. The incidence of post-ERCP pancreatitis varies substantially and is reported to be around 1%-10%, although there are some reports with an incidence of around 30%[2,3]. Usually, it is a mild or moderate pancreatitis, but in some instances it can be severe and fatal[2]. According to a consensus from 1991, PEP is the presence of new pancreatic-type abdominal pain severe enough to require hospital admission or prolonged hospital stay with levels of serum amylase two to three times greater than normal, occurring 24 h after ERCP[4,5]. Although PEP is mostly a mild complication of ERCP, it causes prolonged hospitalization, anatomical complications, and further procedures (endoscopies, laparoscopies, open surgery, *etc.*). It can cause the deterioration of the patient's health, as well as a huge financial burden to hospitals. Therefore, preventing PEP could benefit both patients and hospitals. Attempts at preventing PEP have been carried out using pharmacological prophylaxis, technical measures or proper patient selection.

Prophylactic measures of PEP include pharmacological and mechanical ERCP-related approaches. Mechanical solutions for PEP prevention have been found in prophylactic stenting of the pancreatic duct in high risk patients and early pre-cut cannulation. As a current gold standard, placement of a pancreatic stent is recommended. Nevertheless, endoscopists are looking for a pharmacological solution which will be safe, cheap, easily administered just before the procedure and applicable to all types of patients requiring ERCP.

In this review, we attempt to present and discuss different ways of preventing post-ERCP pancreatitis by reviewing the literature that describes various factors of PEP prevention and the possible utilization of endoscopic techniques and drugs in preventing PEP or lowering its incidence and severity.

PHARMACOLOGICAL PREVENTION

Many pharmacological agents have been considered in the prevention of PEP, although their effectiveness remains debatable. These include allopurinol, gabexate mesylate, octreotide, somatostatin, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and many others. The current literature reveals that basically all of the suggested pharmacological agents have either disappointing or inconclusive results so far, with the exception of NSAIDs[2,3,6-9].

Nitrates

Some potential in the prevention of PEP has been observed for glyceryl nitrate (GTN). Due to his dilatatore properties, it is believed that its usage could relax biliary and pancreatic sphincters, thus alleviating cannulation of the common bile duct (CBD). GTN can reduce the pressure of the sphincter of Oddi[10]. If used during and after ERCP, GTN can relax pancreatobiliary sphincters, facilitating CBD cannulation and reducing the chances of obstruction of the pancreatic outflow. GTN is also cost effective and easily administered. A meta-analysis was conducted exploring the aforementioned effects of GTN. More precisely, Chen *et al*[11] investigated the effect of prophylactic administration of GTN on the incidence of PEP, and the success of cannulation of the CBD duct. They conducted the analysis on a total number of 1841 patients. Out of the total number, 150 patients developed PEP; 55 were given GTN and 95 were given a placebo. They found a statistically significant difference in risk for acquiring PEP between the group who received GTN and the placebo group. They also analyzed the route of administration of GTN, and found that there were 10/128 patients (7.8%) who developed PEP after sublingual administration of GTN in comparison to 26/132 patients in the placebo group. On the other hand, transdermal application of GTN was less successful, and PEP developed in 32/626 (5.1%) patients, whereas 50/640 (7.8%) patients in the placebo group acquired PEP. They concluded that sublingual administration of GTN had a better success rate in prevention of PEP. The second aim of their analysis was to determine if GTN contributes to a more successful cannulation. They found five and seven articles with 900 and 1294 patients, respectively, in which they did not find any significant differences, meaning that prophylactic administration of GTN has no effect on facilitating bile duct cannulation. Wehrmann *et al*[12] also concluded that there was no difference between a group which received GTN and a group which received placebo in time needed for successful cannulation and the number of cannulation attempts. They concluded that topical administration of GTN

does not alleviate cannulation of the bile duct during ERCP. The only adverse effects worth mentioning were hypotension and headache, both easily treated with intravenous administration of crystalloids. Chen *et al*[11] concluded: (1) GTN administration can prevent PEP and reduce its incidence; (2) GTN does not facilitate cannulation of the CBD; and (3) GTN is effective, cheap and easily administered.

There are other conflicting findings regarding the efficacy of GTN in PEP prophylaxis. Kaffes *et al*[13] conducted a prospective, double-blind, placebo-controlled trial in which they evaluated the effect of GTN on the prevention of PEP and success rates of cannulation during ERCP. They included a total number of 318 patients divided into two groups-one on a GTN transdermal patch (155 patients) and the other receiving placebo. There was no notable distinction between the two groups considering the success of initial cannulation, deep cannulation, time needed to achieve successful cannulation, usage of the needle knife or guide wire and PEP. Following their results, they concluded that transdermal GTN had no effect on the prevention of PEP or improvements in cannulation success rates. On the other hand, Bai *et al*[14] performed a meta-analysis of randomized, double-blind, placebo controlled trials evaluating the prophylactic properties of GTN in PEP prevention. They analyzed eight studies with a total of 1920 patients and found that GTN treatment significantly lowered the incidence rate of PEP; incidence of PEP in the GTN group and placebo group was 5.9% and 9.8%, respectively. Also, patients who received GTN had a 39% less chance of acquiring PEP.

Another, similar meta-analysis was performed by Ding *et al*[15].They included 12 randomized, controlled trials with 2649 patients; 11 of those trials reported the occurrence of PEP and compared GTN's and placebo's effect on PEP prevention. The results showed an overall incidence of PEP of 8.8% with a PEP incidence of 7.1% and 10.5% among GTN and placebo patients, respectively. They also conducted a sub-group meta-analysis comparing transdermal and sublingual application of GTN with the results suggesting that sublingual administration of GTN had far more success in prevention of PEP. In conclusion, their results indicated that GTN administration is an effective prophylactic measure in the prevention of PEP. An interesting approach has been made by a group of Iranian authors. Sotoudehmanesh *et al*[16] conducted a randomized trial with a combination of sublingual nitrates and indomethacin *vs* indomethacin alone as a method of preventing PEP. They reported RR = 0.39, 95%CI: 0.18-0.96, P = 0.016, favoring the combination therapy. Drug-induced adverse events were equal among the study groups. They suggested that the aforementioned combination of drugs is more effective in reducing PEP incidence than indomethacin by itself. In conclusion, GTN is not recommended for routine use in PEP prophylaxis but GTN in combination with some other agent such as NSAIDs may further reduce PEP incidence. Further research is needed in order to confirm and support these findings.

Heparin

A group of Chinese authors[17] performed a review and a meta-analysis of clinical trials on the potential beneficial properties of low-dose heparin in the prevention of PEP. Heparin has proven beneficial effects in acute pancreatitis in animals. Low-molecular-weight heparin (LMWH) promotes the survival rate and decreases mortality in cases of severe acute pancreatitis. It also reduces the severity of pancreatitis related microcirculatory disorders in rats. In combination with insulin, heparin is beneficial in acute hyperlipidemic pancreatitis. However, there is conflicting data about its prophylactic effect. In their review Li *et al*[17] analyzed seven studies with a total number of 1438 patients. The incidence of PEP was 5.65% in the group which was given heparin and 7.91% in the control group. Severe PEP occurred in eight cases; 2/562 (0.35%) in the heparin group and 6/872 (0.69%) in the control group. Post-ERCP hemorrhage occurred in 23 patients; 8/562 (1.42%) in the heparin group, and 15/872 (1.72%) in the control group. These results showed no significant correlation between the use of heparin and reduction inPEP incidence. There was no connection between the use of heparin and post-ERCP hemorrhage; low doses did not worsen post-ERCP hemorrhage. They also compared low dose unfractioned heparin and low dose LMWH, finding no difference in the success of PEP reduction, reduction in the severity of PEP, or hemorrhage complications after ERCP. However, Rabenstein *et al*[18] produced results showing significant success in lowering PEP incidence in patients using heparin. They conducted an analysis on 815 patients that underwent ERCP and sphincterotomy. Heparin was given to 268 patients, while the rest of the patients, precisely 547 of them formed the control group. The incidence sof PEP were 3.4% and 7.9%, in the heparin group and the control group, respectively. Furthermore, heparin did not increase hemorrhagic complications. Based on their findings, they concluded that heparin administration correlated with a significantly lower incidence of PEP.

Ung *et al*[19] also conducted a randomized, double-blind, placebo-controlled trial over 89 patients. They were randomly given either 0.2 mL of 25000 IE of heparin or 0.2 mL of saline subcutaneously 4 h before and 4 and 18 h after ERCP. They found that patients which were given heparin had no elevations in levels of amylase, ALT and AST. They concluded

that heparin reduces the increase in amylase levels which is typical for PEP. Li *et al*[17] concluded that neither low dose unfractioned heparin nor LMWH had a significant impact on reducing PEP incidence or its prevention. Despite some promising results where the beneficial effects of heparin were emphasized, this is still not a recommended prevention method. In addition to GTN and heparin, there are several other potential chemoprophylactic agents considered to be beneficial in the prevention of PEP.

Somatostatin and protease inhibitors

Somatostatin is a drug considered to have a beneficial effect on PEP prevention. It inhibits the secretory functions of the pancreas. It can also restrain the motility of the sphincter of Oddi. This combined action can contribute to PEP prevention. The problem with somatostatin is that it has a short half-life and has to be continuously administered intravenously. Due to those disadvantages, octreotide, a somatostatin analogue is used. It has a half-life of 3 h, and can be administered subcutaneously. Arcidiacono *et al*[20] conducted a study on 151 patients who were randomly divided into two groups. Group A (75 patients) was given 0.1 mg of octreotide subcutaneously 120 and 30 min before and 4 h after endoscopy, while group B (76 patients) was given a placebo (1 mL of saline).

They measured serum amylase levels before octreotide administration and 4, 24 and 48 h after ERCP. Group B had a greater rise in serum amylase levels, but the statistically significant difference was measured only 48 h after ERCP. Both groups had five cases of pancreatitis and two cases of cholangitis. Overall, octreotide administration showed no advantages in the prevention of PEP. On the other hand, octreotide contributed to less severe cases of pancreatitis in the treated group, although the difference was not statistically significant. Further research should be conducted, especially on high risk patients.

In relation with somatostatin, a randomized, prospective, double blinded trial was conducted by Katsinelos *et al*[21] on a total number of 540 patients divided into group A and group B in order to see the potential benefits of administering a combination of somatostatin and diclofenac sodium in the prevention of PEP. Both groups had the same number of patients, patients in group A received 1.5 mg of somatostatin intravenously diluted in 500 mL of saline solution 30 min before and 6 h after ERCP. They also received a suppository of 100 mg diclofenac sodium 30-60 min prior to ERCP. Patients in group B received 500 mL of saline and placebo suppositories which were same in appearance as diclofenac sodium suppositories. Patients who had complications or adverse reactions during ERCP, such as hypotension, intolerance to somatostatin or placebo, drop in oxygen saturation, or inability to reach the papilla, were excluded from the study. Cannulation of the common bile duct was performed by a sphincterotome. If unsuccessful after 5 min, a guide wire was used. In cases where guide wire cannulation failed after 5 min, pre-cut papillotomy was performed. A sphincterotome with guide wire cannulation time over 5 min was deemed difficult cannulation. They defined PEP according to the consensus from 1991[4]. PEP was graded as "mild" if lasting 3 d, "moderate" if therapeutic measures were required for 4 to 10 d after ERCP and "severe" if complications lasted longer than 10 d or if death occurred. Also, PEP was severe if a CT scan showed the presence of tissue necrosis in > 30% of the pancreas or if it showed peripancreatic fluid.

The aims of this study were to determine whether the aforementioned combination of drugs could prevent PEP and affect the type of PEP and side effects caused by the same combination[21]. The advantage of this study was that both groups were comparable in sex, age, indications for therapeutic ERCP and ERCP findings. Also, there was no significant difference in cannulation difficulty, pancreatic opacification, number of guide wires inserted, and use of pre-cut papillotomy.

After data analysis, the overall PEP incidence was 7.2%, occurring in 39 patients. Mild PEP occurred in 29 patients (5.6%), moderate in 8 (1.5%) and severe PEP in 2 patients (0.4%). They found a significant difference between the two groups in the rate of PEP: 4.7% in group A and 10.4% in group B. Moreover, the incidence of PEP in high risk patients was significantly lower in the group receiving the diclofenac and somatostatin combination than in the placebo group, *i.e.,* 5.8% and 12.3%, respectively. However, there was no significant distinction in low risk patients (group A 1.5% and group B 3.5%). Based on univariate and multivariate analyses, they found that a history of acute pancreatitis, pancreatic opacification of the first class branches and beyond, and the absence of pharmacoprophylaxis were all independent risk factors for PEP development. Several problems arose in this study. It was difficult to differentiate patients with high and low risk for PEP. There are patient-related factors such as suspected dysfunction of the sphincter of Oddi and previous acute pancreatitis which can be easily identified prior to the procedure. However, ERPC-related risk factors such as difficult cannulation, opacification of the pancreatic duct and pre-cut papillotomy can be identified only during and after ERCP. Logic therefore infers that an ideal pharmacoprophylactic agent has to include all patients undergoing ERCP. Further limitations to this study were the low number of pancreatic sphincterotomes, and only a few suspected sphincters of Oddi dysfunctions (SOD), which are

both known and confirmed risk factors for PEP. Furthermore, ERCP was performed by experienced endoscopists, which contributes to lower rates of PEP.

The protease inhibitors gabexate mesilate, ulinastatin and nafamostat mesilate have been registered for the treatment of acute pancreatitis. The rationale for their usage is a reduction in the pancreatic secretion of proteolytic enzymes. Gabexate mesilate has been shown to decrease the incidence of PEP[22,23], but this agent has to be infused continuously for as long as 13 h because of its short half-life; ulinastatin can be injected as a bolus. Furthermore, Masci *et al*[23] compared two infusion rates of gabexate mesilate; 13 h infusion and 6.5 h infusion. They found no difference in efficacy between the two infusion rates. In a recent meta-analysis by Yuhara *et al*[24], only nafamostat mesilate and NSAIDs showed the potential to reduce PEP, while the other two protease inhibitors were, gabexate mesilate and ulinastatin were shown not to be efficient in reduction of PEP incidence. Due to their high price and inconvenient route of administration, protease inhibitors cannot be recommended as a routine prophylactic measure. Positive results from Japanese trials should be replicated at other centers.

Non-steroidal anti-inflammatory drugs

In some previous studies, it has been pointed out that phospholipase A2 has a pivotal role in the initial inflammatory cascade in acute pancreatitis by regulating a variety of proinflammatory mediators, including arachidonic acid products and platelet-activating factors[25-27]. Murray *et al*[28] was the first one who described the potential of NSAIDs in preventing PEP. These results have been confirmed in several other trials[7,29-32]. Cheon *et al*[29] showed no difference between oral administration of diclofenac and placebo. They conducted a study on 207 patients, 72% of whom were high risk patients (suspected SOD or pancreatic therapy). This suggests that rectal administration of diclofenac has advantages over oral administration. Katsinelos *et al*[21] concluded that a combination of diclofenac and somatostatin significantly lowers the incidence of PEP, especially in high risk patients. Univariate and multivariate analyses confirmed that pre-procedure administration of the mentioned combination is associated with a significantly reduced risk of PEP. They also found no relevant adverse effects of these medications, especially no increases in bleeding after sphincterotomy.

There is more evidence supporting the administration of NSAIDs. Elmunzer *et al*[30] performed a meta-analysis of studies which investigated the efficacy of NSAIDs on the prophylaxis of PEP. They analyzed four studies by Murray *et al*[28], Khoshbaten *et al*[31], Sotoudehmanesh *et al*[16] and Montãno Loza *et al*[33]. First two studies compared rectal administration of 100 mg of diclofenac with placebo, while the latter two compared rectal administration of 100 mg of indomethacin with placebo. Sotoudehmanesh *et al*[32] conducted a trial on 442 patients who were given either indomethacin or placebo just before ERCP. Overall, the PEP incidence was 4.9%, which could be explained by the fact that only 10% of the patients in this trial had SOD. There was no significant difference in the PEP incidence between the placebo group and the indomethacin group, *i.e.,* 3.2% (7/221) and 6.8% (15/221), respectively. However, an additional analysis found that indomethacin had a beneficial effect in patients undergoing pancreatic duct injection. The same group conducted an interesting trial where they compared indomethacin plus sublingual nitrates *vs* indomethacin alone. They reported a further reduction in PEP incidence in the combined group (indomethacin plus nitrates), *i.e.,* RR = 0.39 and 95%CI: 0.18-0.86, which may be of particular interest in high risk patients[16]. None of those patients developed moderate or severe pancreatitis, unlike the seven patients in the placebo group who had developed both modalities. Montãno Loza *et al*[33] conducted the same test with indomethacin and placebo. Their findings were different, and suggested a statistically significant difference in PEP incidence; 5.3% in the indomethacin group and 16% in the placebo group. Murray *et al*[28] and Khohsbaten *et al*[31] conducted research as mentioned previously. They found that the incidence of PEP in the placebo group was higher, making the difference between the two groups statistically significant. Murray *et al*[28] reported a PEP incidence of 6.4% and 15.5% in the diclofenac and placebo groups, respectively, while Khoshbaten *et al*[31] reported a PEP incidence of 15% in the diclofenac group and 26% in the placebo group. No adverse effects were noted in this meta-analysis. Elmunzer *et al*[30] concluded that patients who received NSAIDs were 64% less likely to develop pancreatitis and 90% less likely to develop moderate to severe pancreatitis. Both diclofenac and indomethacin have been proven to be effective in preventing the development of moderate or severe PEP. All of the four studies that were included in this meta-analysis show a positive trend for prophylactic use of NSAIDs.

Furthermore, these studies showed that using NSAIDs is more cost effective. If an institution performs 750 ERCPs annually, and the incidence rate of PEP is 5%, we come to a number of 38 PEPs per year. United States Medicare provides financial support for PEP in the amount of 5700 USD per case, which when multiplied by the number of PEPs comes to 216600 USD per year. The cost of one dose of NSAIDs is between 1.25 and 2 USD. The annual cost of administering diclofenac before every

ERCP would be around 1500 USD, but it would reduce the number of PEPs to 13. Thus, a lower number of PEPs equals a smaller amount of money spent annually; we come to a figure of 74100 USD per PEP. Adding the cost of NSAIDs (1500 USD), the institution would spend 76500 USD, or 141000 USD less than if they were not using NSAIDs. Their meta-analysis supports the use of NSAIDs in PEP prophylaxis, giving an advantage to diclofenac.

Elmunzer *et al*[7] conducted an additional trial concerning the rectal application of NSAIDs. They performed a multicenter, randomized, placebo-controlled, double-blind clinical trial including 602 patients with a high risk of PEP development. A high risk for PEP was established based on previously validated patient-related and procedure-related risk factors. Out of the total number of patients, 493 (82%) had a suspicion of SOD. Patients were divided into two groups: one received a single dose of indomethacin rectally (295 patients) and the other received placebo (307 patients). PEP occurred in 27 patients (9.2%) in the indomethacin group and in 52 patients (16.9%) in the placebo group (P = 0.005). Furthermore, moderate/severe PEP was observed in 13 patients (4.4%) in the indomethacin group and in 27 patients (8.8%) in the placebo group (P = 0.03). They concluded that rectal administration of indomethacin notably reduced the incidence of PEP in patients who were at a high risk of PEP development. At the moment, it is absolutely clear that rectal administration of NSAIDs (diclofenac sodium and indomethacin) is the preferred method for reducing the incidence of PEP. Due to their good safety profile, low price and easy availability, NSAIDs are at this moment the best pharmacological prophylactic method. In the future, we are expecting the results from more randomized controlled trials regarding combination therapy (NSAIDs plus nitrates or antibiotics) and possible further reductions in the incidence of PEP.

Antibiotics

Prophylactic use of antibiotics is recommended by the British Society of Gastroenterology during ERCP in patients who are expected to obtain full patency of the bile duct, patients with advanced hematologic cancer, history of liver transplantation, pancreatic pseudocyst and patients with severe neutropenia. Others recommend antibiotic prophylaxis before ERCP, especially in the presence of biliary obstruction. Antibiotics should decrease or prevent post-ERCP complications, such as cholangitis, cholecystitis, septicemia and pancreatitis. A meta-analysis was conducted by Brand *et al*[34] on nine randomized, controlled trials including 1573 patients. They showed the beneficial properties of antibiotic prophylaxis, but only in patients whose biliary obstruction persisted after ERCP. In patients whose biliary obstruction was resolved, antibiotics did not have much effect. The conclusion was drawn that, although antibiotics show beneficial properties in PEP prophylaxis, the presence or absence of biliary obstruction after ERCP is the determining factor in the efficacy of antibiotics and the incidence of post-ERCP infections.

Antibiotic prophylaxis of PEP is still to be proven and established and there are conflicting viewpoints on this matter. For instance, the American Society for Gastrointestinal Endoscopy recommends antibiotic prophylaxis for ERCP in patients with bile duct obstruction.

Research performed by Räty *et al*[35] suggests that antibiotic prophylaxis effectively decreases the risk of PEP development. They conducted a study on 321 patients, who were divided into two groups: a prophylaxis group and a control group. There were 161 patients in the prophylaxis group; all received 2 g of cephtazidime, and 160 patients in the control group who did not receive an antibiotic. Patients with allergy to cephalosporins, immunodeficiency, clinical jaundice or with any other condition requiring antibiotic usage were excluded. Also, pregnant patients did not participate. The diagnosis of acute pancreatitis was based on increased levels of serum amylase (> 900 IU/L), CRP level, leukocyte count, no increase in liver chemical values and clinical findings. Nine patients in the prophylaxis group (6%) and 15 patients in the control group (9%) had a notable increase in serum amylase levels (> 900 U/L) after ERCP, but only four out of nine patients in the prophylactic group developed clinical signs of pancreatitis, leukocytosis and pain. In comparison, all 15 patients from the control group with hyperamylasemia had pain, elevated CRP, leukocytosis and other signs of pancreatitis. Multivariate analysis showed that lack of antibiotic prophylaxis and sphincterotomy are independent risk factors for the development of PEP. They concluded that the application of antibiotics as chemoprophylaxis effectively decreases the chances of PEP development.

However, in the most extensive review and meta-analysis by Bai *et al*[36] on antibiotic prophylaxis of post-ERCP cholangitis, the authors included seven trials and 1389 patients which were divided into two groups: 705 patients in the control group and 684 in the treated group. Cholangitis occurred in 5.8% of control group patients and 3.4% of treated patients, with no statistical significance. In accordance with the ASGE recommendations for antibiotic prophylaxis, sensitivity analysis was performed targeting patients with suspicious biliary obstruction. It showed that the incidence of post-ERCP cholangitis was 2.8% in patients who received antibiotics and 5.4% in control group patients, suggesting that there is no protective effect of antibiotics. In their

summary, they agreed that antibiotics cannot be used as an effective means of post-ERCP cholangitis prevention.

Although their data showed no correlation between antibiotic prophylaxis and a reduced rate of post-ERCP cholangitis, we can assume that the same premise can be applied to the connection of antibiotic prophylaxis and PEP prevention, *i.e.,* antibiotic administration will not be effective in the prophylaxis of PEP. However, due to the lack of sufficient data on this topic, we believe that further research should be conducted in an attempt to show the potential benefit of antibiotics as chemoprophylactic agents.

Other pharmacological treatments

There are some other pharmacological agents thought to be potentially beneficial in PEP prophylaxis. For example, allopurinol has demonstrated beneficial properties in animal models. However, three trials with human subjects offer conflicting and inconclusive results[37,38]. In two trials, the authors showed benefits from the usage of allopurinol. Kastinelos *et al*[37] gave 600 mg of allopurinol *per os* to their patients 15 and 3 h before ERCP and saw significantly lower rates of PEP in comparison to the placebo group; 3.2% and 17.8%, respectively. Furthermore, patients with pancreatitis who received allopurinol had shorter duration of hospital stay than those who were in the placebo group. Martinez-Torres *et al*[38] gave 300 mg of allopurinol *per os* to 85 patients at same times as in the Katsinelos trial, while the other 85 patients received oral placebo. They observed significantly lower rates in PEP incidence, *i.e.,* 2.3% in comparison to 9.4% in the placebo group. However, Mosler *et al*[39] conducted a trial where they randomly administered allopurinol and placebo 4 h and 1 h prior to ERCP. PEP incidence was 12.96% and 12.14%, in allopurinol and placebo groups, respectively. They concluded that there is no efficacy of allopurinol prophylaxis of PEP.

A new possible treatment to the prevention of PEP is being used by German physicians who recently published a study protocol[40]. They designed a randomized, double-blind, placebo controlled study where they will test the effect of magnesium sulfate on the incidence and severity of PEP. They will include a total of 502 patients distributed into two groups. One group of patients will receive 4930 mg of magnesium sulfate 60 min before and 6 h after ERCP and the other group will receive placebo at the same time intervals. The incidence of PEP and hyperlipasemia, the degree of pain, analgesic usage and the length of hospitalization will be observed and analyzed. Their opinion is that, if successful, magnesium sulfate could become a routinely used a pharmacological prophylactic agent.

There are some alternative approaches with promising results such as aggressive hydration with Ringer's lactate[41,42]. Buxbaum *et al*[41] performed a study in which patients who were undergoing ERCP for the first time were randomly assigned to groups (2:1) that either received aggressive hydration with lactated Ringer's solution (3 mL/kg per hour during the procedure, a 20-mL/kg bolus after the procedure, and 3 mL/kg per hour continuously for 8 h post-ERCP) or standard hydration with Ringer's solution (1.5 mL/kg per hour during and for 8 h post-procedure). They concluded that aggressive intravenous hydration with lactated Ringer's solution reduces development of PEP. Since these are the results of a pilot study with only 62 patients, this benefit has to be shown in trials with an adequate sample size.

Although we have adequate pharmacological agents such as NSAIDs, which can significantly reduce the incidence of PEP, possible new approaches are very welcome. We are eager to see the results from adequately powered trials regarding aggressive hydration. If we get positive results, this may become the easiest preventive method.

Non-pharmacological approaches

Vila *et al*[43] presented an article reviewing the factors contributing to PEP and other post-ERCP complications, such as non-technical factors and technical factors. They also emphasized the role of pancreatic stenting and NSAIDs in PEP prophylaxis as the two methods with the most scientific evidence. Non-technical factors include placement of the pancreatic stent and administration of NSAIDs. Multiple studies have shown the benefits of placing a pancreatic stent.

Pancreatic stent placement

There are many reviews and analyses suggesting the beneficial impact of pancreatic stent placement. Singh *et al*[44] conducted a meta-analysis which included five studies and 481 patients. They showed that the incidence of PEP in the stented group was significantly lower (5.8%) in contrast to the no-stent group (15.5%).They drew a conclusion stating that temporary placement of a stent in the main pancreatic duct lowers risk for PEP. Additional meta-analysis of one more study by Andriulli *et al*[45] showed similar results. They conducted a meta-analysis of 6 controlled studies with an addition of 12 uncontrolled studies. Their results showed that the stented group had a PEP rate of 12% while the control group rate was 24.1%. They also showed a reduction in the number of cases of severe pancreatitis in stented patients. Choudhary *et al*[46] conducted a meta-analysis on eight randomized, controlled trials and 656 patients, and 10 non-randomized studies including 4904 patients. They observed the incidence of PEP, incidence of hyperamylasemia, incidence of mild, moderate and

severe pancreatitis, and possible adverse effects of stent placement. The results of the randomized, controlled studies showed a significant decrease in the PEP incidence in the stented group, *i.e.,* 4.6%. The incidence of PEP in the control group was 19.7%. Furthermore, fewer PEP cases were observed in patients with a stent < 3 cm, but with no statistical significance. No statistically significant difference was noted in using flanged and unflanged stents. Concerning hyperamylasemia, levels were significantly lower in the stented group. Analysis of the non-randomized trials also showed a statistically significant lower incidence of PEP in five trials. Moreover, pancreatic stenting led to fewer cases of severe pancreatitis. Although there is no doubt that pancreatic stents decrease the incidence of PEP, several questions remains unanswered, possibly vital questions which if answered could lower the PEP incidence even more. Who should get a pancreatic stent? What is the best time of placement - before or after therapy, *e.g.,* before sphincterotomy? How long do stents have to remain in place? For now, pancreatic stents are placed in high risk patients. Further research has to be done in order to provide answers to these questions. However, the European Society of Gastrointestinal Endoscopy recommends stent placement in high risk patients undergoing ERCP[2]. High risk patients are, according to a consensus, patients with SOD, young women, patients with previous pancreatitis, and patients with a high number of cannulations and injections of the pancreatic duct during ampullectomy or cannulation. The recommended size of the stent is 5-Fr. Furthermore, pancreatic stents should be placed taking endoscopists's rate of success into consideration, which has to be > 75%[2].

Mazaki *et al*[9] reviewed and conducted a meta-analysis on 8 studies including 680 patients. All studies included different kinds of high risk patients, such as SOD, difficult cannulation, precut sphincterotomy, biliary balloon dilatation of an intact papilla for stone extraction, ampullectomy or pancreatic brush cytology. Pancreatic stent placement had a success rate of 90% to 100% in five studies. Out of the total number of 680 patients, 336 received a pancreatic stent, while 344 were in the control group. Total number of PEPs was 82; 19 patients (6%) in the stent group, and 64 patients (19%) in the control group, which was statistically significant. They also showed that pancreatic stents were more efficient in high risk patients. This meta-analysis showed that pancreatic stent placement is a good and effective prophylaxis for PEP. Furthermore, it is consistent with previously performed meta-analyses[44,45].

Ito *et al*[47] conducted a study on 9192 ERCP procedures. Out of the total number of ERCPs, 414 patients were included in this study as they were high risk patients for the development of PEP. High risk criteria were: female gender, history of pancreatitis, SOD, difficult cannulation of the bile duct, pancreatic duct cytology/biopsy, precut sphincterotomy, pancreatic sphincterotomy and endoscopic ampullectomy. The size of stents used was 5-Fr, 3 cm long with a single pigtail. The goals of this study were to explore the frequency and severity of PEP, the frequency of hyperamylasemia and risk factors for PEP. The incidence of PEP was 9.9% and 90% of those were mild cases. Taking the high risk factors of these patients into consideration, the PEP incidence in this study was acceptable. The frequency of moderate to severe cases of PEP was 10%. In two important studies[48,49], the rates of moderate and severe pancreatitis were 47% and 25%, respectively. In conclusion, the results of this study suggested that pancreatic duct stenting decreases the incidence of PEP, and could possibly contribute to less severe cases of PEP, thereby easing the patient's recovery.

Zolotarevsky *et al*[50] conducted a trial regarding the optimal stent size for insertion into the pancreatic duct for PEP prevention. The current viewpoint on stent size goes in favor of 5-Fr stents. Zolotarevsky *et al*[50] compared 5-Fr and 3-Fr stents in order to see which one led to better results in pancreatic stenting. A large trial by Rashdan *et al*[51] was conducted on 2283 patients who underwent ERCP and had a 3-4-Fr, unflanged stent placed. Incidence of pancreatitis was 7.5% and 10.6% for 3-Fr and 4-Fr stents, respectively in comparison with rates of 9.8% and 14.6% for larger stents, 5-Fr and 6-Fr, respectively. They concluded that smaller sized stents were superior to larger ones in preventing PEP. However, Chahal *et al*[52] showed a completely different situation; 5-Fr stents correlated with higher rates of spontaneous stent passage and lower rates of PEP. In addition, this study showed that placing 3-Fr stents had more failed attempts. Failure in placing a stent can prolong the procedure and thus augment the chances of PEP development. A comparison of 5-Fr and 3-Fr stents done by Zolotarevsky *et al*[50] was performed on 234 patients by random assignment of those stents. Out of the total number of patients, 78 were at high risk for PEP. Pancreatic stent placement was successful in 77 patients. Spontaneous passage rates duringa two-week period were 68.4% and 75% for the 5-Fr and 3-Fr stents, respectively. Lack of stent passage at 2 wk was also nearly the same, *i.e.,* 10.5% and 10% for the 5-Fr and 3-Fr stents, respectively.

Another important aspect in comparison of these two stents and their efficacy was the number of wires needed for stent placement. One wire was sufficient in 22 cases of 5-Fr stent placement (59.4%), whereas 3-Fr stent placement with one wire occurred in only eight cases (20.5%); a

significant difference. The time required to place a stent was more frequently prolonged during the placement of 3-Fr stents. Furthermore, the placement of 5-Fr stents was deemed easier than placing a 3-Fr stent.

Eleven patients (14.1%) developed PEP, which manifested a sa mild or moderate form. There was no statistically significant difference in PEP incidence between the stent groups. In conclusion, an increased number of wires needed for successful stent placement, prolonged attempts for stent placement and a higher number of failed stenting attempts may be associated with a higher incidence of PEP. In this study, the results showed that the technical aspects of the 5-Fr stent render it favorable over the 3-Fr stent; its placement is easier, faster and requires fewer wires. These criteria alone should be enough to give the 5-Fr stent an advantage in choosing the better and more effective stent in pancreatic stent placement. A recent, excellent network meta-analysis has provided definite results regarding some of these dilemmas. Afghani *et al*[53] analyzed 6 randomized, controlled studies including 561 patients. The authors concluded that the 5-Fr stent is superior to the 3-Fr pancreatic stent for the prevention of PEP in high risk patients. Also, the performance of 5 Fr stents was not influenced by the design (flanged, straight, pigtail), suggesting that the diameter is more important for the prevention of PEP than the type of stent.

Despite the robust data which favor the usage of NSAIDs and pancreas stenting in the prevention of PEP, gastroenterologists still have some doubts. Dumonceau *et al*[54] completed a survey about prophylactic pancreatic stenting and NSAID administration. They distributed the survey to 467 medical doctors, but collected only 141 completed ones. The majority of respondents (61.7%) worked in a community hospital where the ERCP volume was $\leqslant$ 500 per year. Diagnostic ERCP was used in < 20% of cases by the majority of respondents (83%). The majority of the respondents did not attempt prophylactic pancreatic stenting in the presence of procedure-related risks for PEP, such as prolonged or difficult cannulation, previous PEP or needle pre-cut. Only in the case of ampullectomy did the majority of respondents (54.5%) attempt pancreatic stenting. They attempted the procedure in more than 50% of cases. However, pancreatic stenting was attempted more frequently when patient-related risk factors were present. Thirty respondents (21.3%) did not attempt pancreatic stenting at all. Those who attempted pancreatic stenting used mainly 5-Fr stents (64.5%). Fourteen of them used either 3-Fr or 7-Fr stents. The majority of respondents, namely 118 of them (83.7%) did not use NSAIDs for PEP prevention; 88.1% of those 118 respondents cited lack of evidence as the main reason.

This survey showed a huge gap between the scientific evidence supporting prophylactic pancreatic stenting and its actual application in practice. The reasons for this are a lack of experience and the difficulty of the procedure itself (pancreatic stenting has the highest degree of difficulty). Many of the respondents have little or no confidence in using NSAIDs due to the lack of supporting evidence. Further investigations into PEP prophylaxis and better and more frequent ERCP education could provide a more stable ground for the implementation of techniques and increasing knowledge of the prevention of PEP.

Cannulation

Other technical factors include techniques used in duct cannulation, sphincterotomy and ampullectomy. Guide wire cannulation is one of these factors, and there are many variations. Guide-wire hovering is a variation of direct cannulation where the guide wire hovers a few millimeters to a couple of centimeters through the catheter or sphincterotome. It is useful in pancreatic cannulation when access through the minor papilla is needed.

The guide wire technique has advantages in comparison to contrast cannulation. For example, Cennamo *et al*[55] conducted a meta-analysis of five randomized controlled studies with 1762 patients who showed that guide wire cannulation improves the cannulation rate from 74.9% to 85.3% and, more importantly, reduces the incidence of PEP from 8.6% to 1.6%. Subsequently, guide wire cannulation is considered to be the standard for cannulation. Another variation is pancreatic stenting after guide wire placement. Fogel *et al*[56] reported a significant difference in the incidence of PEP between pancreatic stent placement followed by needle-knife sphincterotomy and double wire cannulation. Placing a stent led to a PEP incidence of 10.7%, while the double wire technique had a rate of 28.3%. Madacsy *et al*[57] also showed the benefits of stent placement. There were no cases of PEP in stented patients, while the PEP incidence in patients who underwent needle-knife with guide wire cannulation was 43%.

It is well known that pre-cut sphincterotomy increases the rate of PEP. It is still not well-defined regarding what is the best approach: to persistently attempt to cannulate or an early (five to ten minutes) switch to pre-cut. A meta-analysis by Cennamo *et al*[58] analyzed six trials by comparing the rates of cannulation and the incidence of PEP in early pre-cut cannulation and persistent cannulation with a late pre-cut. The analyzed data showed no difference in the success rate, *i.e.,* 90.2% and 89.6%, respectively. However, the incidence of PEP differed significantly. PEP occurred in 2.48% in early pre-cut, while its rate was 5.34% in late pre-cut. Another meta-analysis by Gong *et al*[59] also suggests that early pre-cut is more beneficial in PEP prophylaxis. Debate is still ongoing because two recent meta-

analyses have not provided a consistent answer[60,61]. While one group suggests that the rates of PEP are similar in the pre-cut sphincterotomy group and in the persistent attempt group (OR = 0.58, 95%CI: 0.32-1.05)[61], in the other meta-analysis, the authors claimed to have concluded that the early pre-cut technique decreases the trend of PEP incidence[60]. According to the recent literature, we may conclude that we have an obvious trend towards a reduction in PEP incidence by adopting the early pre-cut approach, but further data are needed.

While it is obvious that the wire-guide cannulation technique and pancreatic duct stenting significantly reduce PEP incidence, we are still lacking data regarding the early pre-cut technique. Endoscopists have dilemmas about continuing with attempts to cannulate and possibly further traumatizing the papilla, which can hamper cannulation later on, or switch to the needle knife early but possibly increase the risk of PEP, bleeding or perforation. With unequivocally positive results regarding early pre-cut, our decision would be easier.

CONCLUSION

In summarizing the prophylactic measures against PEP, we can conclude that only two methods of prophylaxis are currently recommended: pancreatic stent placement and NSAID administration, preferably with diclofenac.

Pancreatic stent placement is a recommended and effective method for preventing PEP today. Much is known of its beneficial properties, the type of stent needed, the duration of stent placement and so on. It is a method which has been proven to be effective. NSAIDs are cheap, can be easily given to patients and have little or negligible adverse effects, making diclofenac and other NSAIDs an attractive approach in PEP prevention, but there is still resistance to its usage due to the lack of reliable supporting evidence and/or the lack of information.

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