Post-endoscopic retrograde cholangio-pancreatography pancreatitis: Is time for a new preventive approach?

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Abstract

Acute pancreatitis is the most common serious complication of endoscopic retrograde cholangio-pancreatography (ERCP) and its incidence may exceed 25% in some high-risk patient subsets. In some patients, pancreatitis may follow a severe course with pancreatic necrosis, multimorbid organ failure, permanent disability and even death. Hence, approaches which minimize both the incidence and severity of post-ERCP pancreatitis are worth pursuing. Pancreatic stents have been used with some success in the prevention of post-ERCP, while so far pharmacological trials have yielded disappointing results. A recent multicenter, randomized, placebo-controlled, double-blind trial has shown that rectally administered indomethacin is effective in reducing the incidence of post-ERCP pancreatitis, the occurrence of episodes of moderate-to-severe pancreatitis and the length of hospital stay in high-risk patients. These results together with the demonstration that rectal administration of indomethacin is not associated with enhanced risk of bleeding strongly support the use of this drug in the prophylaxis of post-ERCP pancreatitis.

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Key words: Endoscopic retrograde cholangiopancreatography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Non-steroidal anti-inflammatory drugs; Indomethacin; Pancreatitis prevention

INTRODUCTION

Physicians sometimes make a strenuous effort to cope with illnesses which develop de novo following diagnostic and/or therapeutic interventions. One example of such a struggle is the management of complications occurring in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), a procedure used to both diagnose and treat diseases of the pancreaticobiliary tree[1-4]. Indeed despite recent advances in technology and experience of gastroenterologists, the use of ERCP can be accompanied by perforation, bleeding and pancreatitis[5-8]. Pancreatitis is the most common complication of
ERCP\textsuperscript{[5,7-10]}; its frequency varies between 1\% and 10\% in average risk patients\textsuperscript{[5,7,11-13]}, but can exceed 20\% in high-risk patient subset\textsuperscript{[14-16]}.

**DIAGNOSIS, SEVERITY AND RISK FACTORS OF POST-ERCP PANCREATITIS**

The diagnosis of post-ERCP pancreatitis is based on the presence of pancreatic-type abdominal pain, increase in serum amylase at least 3 times above the upper limit of normal 24 h after the procedure and need of hospitalization or prolongation of a planned hospital admission\textsuperscript{[7]}. Although various criteria have been used to define the severity of pancreatitis\textsuperscript{[17-21]}, the length of hospitalization is now considered a major factor in the evaluation of disease severity. Mild pancreatitis is defined as need for an unplanned hospital stay or an extension of a planned hospital stay by 2-3 d; moderate pancreatitis requires 4-10 d of hospitalization and severe pancreatitis results in a hospitalization of > 10 d. Additionally, pancreatitis can be defined severe if it leads to the development of pancreatic necrosis or pseudocyst, or requires percutaneous or surgical intervention\textsuperscript{[7]}. While most patients develop a mild pancreatitis with rapid and full recovery, a small percentage may follow a severe course with pancreatic necrosis, multiorgan failure, permanent disability, and even death\textsuperscript{[7,11,12,22]}. Hence, approaches which minimize both the incidence and severity of post-ERCP pancreatitis are worth pursuing. Some patient-related (i.e., known or suspected dysfunction of sphincter of Oddi, female gender and previous pancreatitis) and procedure-related (i.e., precut sphincterotomy, pancreatic injection, ampullectomy) characteristics are definite independent risk factors for post-ERCP pancreatitis and may be useful for the stratification of patients into low-risk or high-risk categories\textsuperscript{[23]}. Further factors which may influence the outcome of ERCP and the risk of post-ERCP pancreatitis include availability of equipment and adequacy of endoscopic, radiologic and nursing support\textsuperscript{[24]}. 

**PATHOGENESIS AND PREVENTION OF POST-ERCP PANCREATITIS**

Various types of injury (i.e., mechanical injury to the papilla from cannulation, chemical injury due to ionic contrast agents, hydrostatic injury as a result of excessive contrast injection and thermal injury from electrocautery), developing during the procedure, can impair the drainage from the pancreas and favor activation of factors that cause tissue damage\textsuperscript{[23,25-28]}. Although the exact mechanism driving post-ERCP pancreatitis is not fully understood, circumstantial evidence suggests that, once activated, the pathways of inflammation promote intraluminal activation of proteolytic enzymes, autodigestion of the organ, impaired acinar secretion, and then massive synthesis of chemokines and proinflammatory cytokines, which amplify the ongoing inflammatory process\textsuperscript{[23,25-28]}. Strategies that interrupt one or more of these critical steps could help prevent post-ERCP pancreatitis. There is a wide consensus among gastroenterologists that the ideal pharmacological agent for preventing post-ERCP pancreatitis should have a short administration time, be well tolerated with a low side-effect profile and cost-effective.

The anti-inflammatory activity of indomethacin was first described in 1963, and the drug has been used to treat several rheumatological conditions including osteoarthritis and rheumatoid arthritis\textsuperscript{[25,31]}. Indomethacin shares important pharmacological properties with other non-steroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, and inhibits cyclooxygenase, phospholipase A2 and neutrophil-endothelial interactions, which are supposed to play a major role in the pathogenesis of pancreatitis\textsuperscript{[12,32]}. Previous reports have shown that NSAIDs, including indomethacin, reduce experimental pancreatitis-driven lethality in rodents\textsuperscript{[25,33]} and rectal indomethacin decreases the number of d with pain and number of opiate injections in patients with acute pancreatitis\textsuperscript{[34,37]}. Moreover, three recent meta-analyses\textsuperscript{[38-40]} of four prospective randomized placebo-controlled trials showed that rectal administration of 100 mg diclofenac immediately after the procedure or 100 mg indomethacin immediately before the procedure was effective in reducing pancreatitis, with a pooled relative risk after administration of 0.36 (95\% CI: 0.22-0.60)\textsuperscript{[35,41-43]}. Further analysis showed that prevention of post-ERCP pancreatitis by NSAIDs occurred in patients with either low-risk or high-risk. In particular, Murray et al\textsuperscript{[42]} showed that 100 mg of rectal diclofenac administered to high-risk patients (i.e., patients undergoing pancreatography or with manometrically documented sphincter of Oddi dysfunction) upon arrival in the recovery area significantly reduced the incidence of post-ERCP pancreatitis [7/110 (6.4\%) vs 17/110 (15.5\%) in the placebo group]. Similarly, Khoshbaten et al\textsuperscript{[43]} showed that 100 mg of rectal diclofenac administered to high-risk patients upon arrival in the recovery area was superior to placebo in reducing the incidence of post-ERCP pancreatitis [2/50 (4\%) vs 13/350 (26\%) in the placebo group]. Along the same line is the paper published by Elmunzer et al\textsuperscript{[44]} in a recent issue of *The New England Journal of Medicine* showing that rectally administered indomethacin significantly reduces the incidence of post-ERCP pancreatitis in high-risk patients. The authors performed a multicenter, randomized, placebo-controlled, double-blind trial in which 602 patients were assigned to receive a single dose of rectal indomethacin (100 mg) or placebo immediately after ERCP\textsuperscript{[44]}. The selected patients showed an increased baseline risk of post-ERCP pancreatitis on the basis of patient- and procedure-related independent risk factors (i.e., sphincter of Oddi dysfunction, a history of post-ERCP pancreatitis, pancreatic sphincterotomy and ampullectomy). Overall 79/602 (13.1\%) patients developed post-ERCP pancreatitis and this complication was more frequent in patients receiving placebo [52/307 (16.9\%)] than in those treated with indomethacin [27/295 (9.2\%)]. Moreover, indomethacin reduced the occurrence of episodes of moderate-to-severe pancreatitis [13 (4.4\%)].
27 (8.8%) in the placebo group. Consequently, the median length of hospital stay was 0.5 d shorter in the group of patients treated with indomethacin[41]. Interestingly, in accordance with previous studies evaluating NSAIDs in the prevention of post-ERCP pancreatitis[6,38], the benefit of rectal administration of indomethacin was not associated with enhanced risk of bleeding, as this event was documented in 4 patients receiving the active drug and 7 of those receiving placebo[41].

As mentioned above, a known or suspected dysfunction of sphincter of Oddi is an independent risk factor for post-ERCP pancreatitis.[39,40,41]. The term sphincter of Oddi dysfunction is used to define motility abnormalities caused by stenosis or dyskinesia of the sphincter of Oddi. Both alterations can account for obstruction to flow through the sphincter of Oddi thereby promoting retention of bile in the biliary tree and pancreatic juice in the pancreatic duct and clinical manifestations[42,43]. Dysfunction of sphincter of Oddi can be classified as biliary types I, II and III and pancreatic types I, II and III[44]. The features of biliary-type I include biliary-type abdominal pain, liver enzyme elevation and common bile duct dilatation > 9 mm. Patients with biliary-type II dysfunction have pain and only one of the remaining criteria, while biliary-type III patients have only recurrent biliary-type abdominal pain. Patients with pancreatic-type I dysfunction have pancreatic-type abdominal pain and a dilated pancreatic duct and elevated pancreatic enzymes, or recurrent acute pancreatitis. Pancreatic-type II dysfunction is defined as pancreatic-type abdominal pain and a dilated pancreatic duct or elevated pancreatic enzymes, while type III patients have recurrent pancreatic-type pain alone. Elmunzer et al[44] showed that indomethacin was effective in preventing post-ERCP pancreatitis regardless of whether patients had sphincter of Oddi dysfunction and that the treatment was protective in all the 3 subtypes of sphincter of Oddi dysfunction. However, 82% (495/602) of patients enrolled into the trial had clinical suspicion of sphincter of Oddi dysfunction and more than half of them had manometric alterations compatible with sphincter hypertension. Since this high rate of sphincter of Oddi dysfunction is not representative of most ERCP populations, further experimentation should be performed on large numbers of patients with no sphincter of Oddi dysfunction in order to ascertain whether indomethacin is really effective in this subset of patients. The protective effect of indomethacin did not appear to be influenced by the necessity of performing pancreatic stenting, as well as by additional patient-related (age < 45 years, female gender, history of post-ERCP pancreatitis, history of recurrent pancreatitis), procedure-related (i.e., difficult cannulation, precut sphincterotomy, pancreatic sphincterotomy, pancreatic acinarization, biliary sphincterotomy, ampullectomy) and operator-related (i.e., trainee involved in stenting) characteristics. Other issues which need to be clarified relate to the time of administration and dose of the drug. The Elmunzer’s study shows that the number of patients who need to be treated with indomethacin to prevent one episode of pancreatitis is 13[44]. This could reflect the fact that the time of administration was not appropriate. The indomethacin suppositories were administered immediately after ERCP[44,45]. Plasmatic peak of NSAID concentrations occurs within 30 min from rectal administration, a time-frame which could be sufficient to trigger pancreatitis by ERCP. Previous studies have documented a positive result in post-ERCP pancreatitis reduction even when rectal indomethacin was administered immediately pre-procedure[15,44,46]. We can thus speculate that a double administration of the drug, both before and after ERCP, may be more effective than a single administration. Moreover, dose-response studies would also be necessary as so far all the studies have been performed using 100 mg of drug.

**CONCLUSION**

Data of the present study advance our understanding of how we can prevent post-ERCP pancreatitis, even though additional studies are needed to optimize the dose and time of administration of indomethacin and verify whether the prophylactic effect of the drug can be generalized to all patients with elevated baseline risk of pancreatitis or restricted to particular subgroups.

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