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FIELD OF VISION

NSAIDs for prevention of pancreatitis after endoscopic retrograde cholangiopancreatography: Ready for prime time?

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Abstract

Acute pancreatitis is the most common and the most fearful complication of endoscopic retrograde cholangiopancreatography (ERCP). Prevention of post-ERCP pancreatitis has therefore been of great interest to endoscopists performing ERCP procedures. So far, only pancreatic duct stenting during ERCP and rectal administration of a non-steroidal anti-inflammatory drug (NSAID) prior to or immediately after ERCP have been consistently shown to be effective for prevention of post-ERCP pancreatitis. This commentary focuses on a short discussion about the rates, mechanisms, and risk factors for post-ERCP pancreatitis, and effective means for its prevention with emphasis on the use of NSAIDs including a recent clinical trial published in *The New England Journal of Medicine* by Elmunzer *et al*[11].

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

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INVITED COMMENTARY ON HOT ARTICLES

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP)[1,2]. It is important to distinguish between acute pancreatitis and hyperenzymemia after ERCP. Hyperenzymemia, defined as asymptomatic elevation of serum levels of amylase and lipase, is estimated to occur in more than 75% of patients undergoing ERCP and by itself does not have any clinical consequences[3]. Acute pancreatitis, on the other hand, is less common and can have significant clinical consequences. Although both conditions are characterized by elevation of serum levels of amylase and lipase, diagnosis of acute pancreatitis requires an additional factor, either pancreatic type pain or cross-sectional imaging confirming pancreatic inflammation[4].

Proposed underlying mechanisms that alone or in combination can induce post-ERCP pancreatitis (PEP) are prolonged manipulation around the papillary orifice causing edema, enzymatic injury from intestinal contents or contrast, hydrostatic injury from over-injection of the pancreatic duct, and thermal injury from electrocautery. There are probably other mechanisms involved that are yet to be recognized.

In most patients, the risk of PEP is in the range of 1%-10%. In high-risk cases, the risk can be as high as 30%[1]. Factors that convey a high risk for PEP can be

classified as patient-related, procedure-related, operator-related, and disease- or indication-related. Patient-related factors associated with a higher risk of PEP are younger age, female gender, and a normal serum bilirubin level. Procedure-related factors that have been suggested to be related to a higher risk of PEP include difficult cannulation, balloon dilatation of the biliary sphincter, and injection of contrast into the pancreatic duct particularly when acinarization occurs. Operator-related factors include lack of a good technique, lack of experience, and low case volume. The disease or indication for the ERCP is also important. For example, while the risk of PEP in patients undergoing ERCP for chronic calcific pancreatitis is very low, nearly one in 3 patients with type 3 sphincter of Oddi dysfunction undergoing ERCP will develop PEP.

Acute pancreatitis after ERCP is not a uniform disorder and varies in intensity[1,5]. Most cases of PEP are mild and resolve with proper treatment without any permanent sequela. A minority of the cases, however, is severe. Severe PEP is a feared complication of ERCP and can result in significant morbidity and mortality. Prevention of PEP has therefore been of major interest to endoscopists and significant time and effort have been devoted to finding endoscopic or pharmacologic means of preventing PEP.

So far, only pancreatic duct stenting and use of non-steroidal anti-inflammatory drugs (NSAIDs) consistently have been shown to be effective for PEP prophylaxis.

The first randomized trials assessing pancreatic duct stenting at the time of ERCP for PEP prevention were conducted in the 1990s[1]. Subsequent studies confirmed the effectiveness of this approach in decreasing the rate and severity of PEP, especially in high-risk patients.

Use of NSAIDs for PEP prophylaxis is relatively new. The rationale of NSAIDs administration for PEP prevention lies in their ability to inhibit substances such as prostaglandins, phospholipase A2 and neutrophil-endothelial interaction, which are believed to play an important role in severe inflammatory processes including acute pancreatitis[6]. The first clinical trial assessing the efficacy of a rectally administered NSAID for PEP prevention was reported in 2003 by a British group[7]. In that study, pancreatitis occurred in 6.4% of patients in the NSAID group compared to 15.5% in the placebo group. Two subsequent clinical trials by two independent Iranian research teams found that rectally administered NSAIDs were effective for PEP prevention[8,9]. A Mexican study confirmed those results[10].

The most recent clinical trial on use of a rectally administered NSAID for prevention of post-ERCP pancreatitis was published a few weeks ago[11]. In this clinical trial, 602 patients at elevated risk for post-ERCP pancreatitis were randomly assigned to receive a single dose of rectal indomethacin or placebo immediately after ERCP. The incidence of post-ERCP pancreatitis was significantly reduced among those receiving rectal indomethacin (9.2%) compared to those in the placebo group (16.9%).

In conclusion, based on the current literature, two prevention modalities have proven effective for PEP prophylaxis: (1) endoscopic placement of a pancreatic duct stent during ERCP; and (2) rectally administered NSAID immediately before or after ERCP.

Endoscopic pancreatic duct stenting for PEP prophylaxis in high-risk patients is a well-accepted strategy and is being used as a routine practice in most ERCP centers.

Although still not adopted as a routine practice, there is enough evidence to support the routine use of NSAIDs for PEP prevention at least in high-risk patients.

Although use of endoscopic and pharmacological means such as pancreatic duct stenting or rectally administered NSAIDs can decrease the rate and severity of PEP, they cannot, and should not replace the common sense. The best strategy for prevention of post-ERCP pancreatitis has been and remains avoiding unnecessary procedures. Other strategies for PEP prophylaxis include proper training of the endoscopists and assistants; adequate case volume to maintain proficiency; avoiding repeated injection to the pancreatic duct if evaluation of the pancreatic duct is not required; and referral of high- risk cases to specialized ERCP centers.

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