



Nonsteroidal anti-inflammatory drugs: perhaps not the panacea for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis

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Despite the fact that acute pancreatitis as a complication of endoscopic retrograde cholangiopancreatography (ERCP) was once regarded as unpredictable and inevitable, it is nowadays broadly preventable. Significant advances were achieved in comprehending risk factors and implementing strategic steps to decrease incidence of such a detrimental adverse event. Risk factors and hence preventive strategies concerning post-ERCP pancreatitis (PEP) could be divided in five principal categories.

Patient-related factors

Historically, rates of PEP in prospective studies involving ERCPs and sphincterotomies were approximately 5% in mixed-risk patient cohorts and as high as 20% in truly high-risk cohorts, e.g., those with suspected sphincter of Oddi dysfunction (SOD) (1-3). A lot of other PEP risk factors have been recognized, including younger age, female gender, previous history of PEP, and absence of obstructive jaundice. Protective factors include advanced chronic pancreatitis. Risk factors are additive and possibly synergistic. Patients who are least indicated for conventional ERCP are, ironically, at the highest risk of adverse events. Such an observation directs to an obvious strategy of being particularly cautious at avoiding ERCP in patients with unclear indications and to refrain from interventions with no clear benefit. Endoscopic ultrasound and magnetic resonance cholangiopancreatography, together with proper

clinical reasoning, should facilitate the process of selecting appropriate patients to undergo ERCP, particularly in a community setting.

Procedure-related factors

Difficult cannulation and pancreatic duct (PD) contrast instillation have long been recognized to increase risk, but more recently, deep PD wire passage without PD stent placement has emerged in multiple studies as a dominant factor (1-7)—something that is not widely recognized. Guidewire cannulation has been proven to decrease chances of PEP in comparison with solely catheter-and injection-based techniques, even though its efficacy in high-risk cohorts is questionable and deep pancreatic guidewire passage is the dominant risk factor when utilizing that technique (5,7). A strategy to decrease incidence of technique-related PEP thus condenses to expertise at cannulation, mainly refraining from inadvertent pancreatic manipulations whenever feasible in average-risk biliary indications or performing pancreatic stenting following guidewire passes into PD (6). Precut sphincterotomy seems as a very operator-dependent method with best results when done by an expert endoscopist and combined with PD stenting (8).

Pancreatic stenting

Pancreatic stenting using small-caliber prophylactic stents

is the most extensively studied and effective method for PEP prevention. PD stenting has been proven to decrease incidence of PEP by 60–80%, currently based on more than 10 studies in high-risk patients and 2 studies comprising subjects at low-to-mixed risk of PEP; a recent meta-analysis, the first one to include studies comprising lower-risk patients, demonstrated that PD stenting lowers the risk of mild and moderate as well as severe PEP (9,10). PD stent placement is being increasingly done in routine ERCP and proved to be cost-effective in high-risk patient cohorts. PD stenting is usually straightforward in patients with an inadvertent guidewire access into PD during attempted biliary cannulation. PD stent placement as a strategy carries several limitations including challenging anatomy of the PDs, unfamiliarity, and potential injury especially caused by failed attempts (11). In order to increase success and safety of PD stenting, we propose that endoscopists get familiar with advanced techniques for pancreatic stenting, frequently necessitating small-caliber guidewires and an array of stents and techniques tailored to PD rather than biliary applications. An expansive variety of educational materials to improve technique and safety of biliary access can be found at the official website of the American Society for Gastrointestinal Endoscopy (www.asge.org) including one by the current authors (Video #035).

pH (Fluids)

A novel approach involves pre- or post-procedural hydration generally with lactated Ringer's solution so as to prevent or reduce severity of PEP. Initial results are promising but probably reflect treatment of mild pancreatitis rather than true prevention as most of the studies involved sustained infusion for up to 8 hours post procedure—an impractical approach for increasingly resource-burdened health care systems (12).

Pharmacologic prophylaxis

A safe and inexpensive agent to prevent PEP has been a long-sought-after target that has received a lot of attention in the past decade. Rectally-administered nonsteroidal anti-inflammatory drugs (NSAIDs) are proven to lower risk of PEP by approximately 50%, with multiple positive randomized control trials confirmed by a large number of meta-analyses (13). Limitations of the rectal NSAIDs studies are that most trials were carried out in low- to mixed-risk patient cohorts and that one study involving truly high-risk

patients used pancreatic stents as well in most (82%) of the patients (14); a major concern about NSAIDs is that while they reduce the overall incidence of PEP, they may not be sufficient alone to prevent severe or necrotizing pancreatitis, especially from traumatic obstruction of pancreatic outflow resulting from thermal injury or PD injury from guidewire manipulation. A question undergoing investigation at present is whether the effectiveness of NSAIDs alone is adequate to replace PD stents (15). A study from Iran suggests that NSAIDs plus PD stenting is not superior to NSAIDs alone, although the surprisingly high background rate of pancreatitis (approaching 15%) despite standard biliary obstructive indications in the large majority of cases raises concern about technical expertise at placement of PD stents (16).

In the preceding context, Fogel and colleagues report a very large randomized trial to test the hypothesis that if some rectal NSAIDs are effective, then a higher dose including a 4-hour post-procedure booster dose would be more effective yet (17). In this study, more than 1,000 patients deemed high risk of PEP after the procedure, as risk stratification combined pre- and intraprocedural variables, were enrolled. Of note, about 2/3 patients had the risk factor of suspected SOD, including type III which has now been eliminated as an indication for ERCP based on the results of the EPISOD trial, which was published 10 months after the start of the study (18). Three out of four patients in this trial received a protective pancreatic stent. It is not stated whether the other fourth of patients were not attempted or had a failed PD stent placement, a potentially important variable (11).

The principal findings of the study were that increasing and boosting a postprocedural dose of rectal NSAIDs made no difference in the incidence or severity of PEP.

Rates of pancreatitis were relatively high at 14% overall, with no significant difference between the groups. There were a number of cases of severe PEP, but unfortunately it was not reported whether those patients received protective pancreatic stents or aggressive IV fluid resuscitation.

The high rate of PEP is only somewhat surprising given the case mix including so many patients with SOD in this study. It is surprising in that the current rates of PEP under 5% are achievable at advanced centers with a somewhat lesser prevalence of SOD (19).

The generalizability of this study, like the seminal NEJM study that launched NSAIDs as standard practice (14), is limited by the inclusion of so many patients with SOD type III as a primary indication, a now defunct contraindication

rather than indication for ERCP (18), and performance of the majority of cases at the very same single tertiary center.

How do we interpret this study and the role of NSAIDs: Alone, NSAIDs, regardless of dose, do not seem to be a uniquely effective prevention of PEP. They are not a panacea. A recent network meta-analysis suggests that pancreatic stents appear to be the most effective single strategy when comparing pharmacoprophylaxis and endoscopic stenting (10).

The best solution currently seems to be integration of all 5 approaches mentioned above. Avoid marginal procedures, refine technique, place PD stents whenever deep pancreatic wire passage occurs, give the standard dose of rectal NSAIDs whenever feasible and not contraindicated, and consider aggressive intravenous hydration with lactated Ringer's solution before, during, and after the procedure as long as risk assessment and patient outcome dictate. How these approaches are knitted together probably remains to be refined and will not be the same for all endoscopists, all patients, and all practices.

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