

Indomethacin for post-endoscopic retrograde cholangiopancreatography pancreatitis prophylaxis: Is it the magic bullet?

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Abstract

Acute pancreatitis is a common complication of endoscopic retrograde cholangiopancreatography (ERCP). Pancreatic duct stent insertion after ERCP has been widely accepted as the standard of care for the prevention of this complication in high-risk patients. Unfortunately, the placement of pancreatic stents requires higher level of endoscopic expertise and is not always feasible due to anatomic considerations. Therefore, effective non-invasive pharmacologic prophylaxis remains appealing, particularly if it is inexpensive, easily administered, has a low risk side effect profile and is widely available. There have been multiple studies evaluating potential pharmacologic candidates for post-ERCP pancreatitis (PEP) prophylaxis, most of them yielding disappointing results. A recently published large, multicenter, randomized controlled trial reported that in high risk patients a single dose of rectal indomethacin administered immediately after the ERCP significantly decreased the incidence of PEP compare to placebo.

INVITED COMMENTARY ON HOT ARTICLES

Acute pancreatitis is the most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP). The incidence of post-ERCP pancreatitis (PEP) varies between 1%-10%, with incidence exceeding 25% being reported in certain high-risk patient populations^[1,2]. The wide range for this incidence is mostly due to the heterogeneous interplay of patient characteristics, procedure-related, and operator-related factors^[3,4].

Numerous agents and interventions have been studied so far in the prevention of PEP. These can be divided into sphincter relaxants, protease inhibitors, types of contrast, anti-inflammatory/anti-oxidant agents, anti-secretory agents, electrosurgical techniques, and placement of various types of pancreatic stents^[5]. The results have generally been disappointing and at present the only fea-

sible option to decrease the rate of PEP is the insertion of pancreatic stent in high risk patients. Unfortunately, the placement of pancreatic stents requires higher level of endoscopic expertise and is not always feasible due to anatomic considerations. Indeed, a recent survey reported that more than 20% of physicians performing ERCP never place pancreatic stents^[6]. Therefore, effective pharmacologic prophylaxis remains appealing, particularly if it is inexpensive, easily administered, has a low risk side effect profile and is widely available. Intravenous gabexate, a protease inhibitor, and somatostatin, an anti-secretory agent, have been shown to prevent PEP^[7]. However, both of these therapies are not readily available and require continuous intravenous infusion. As such, the search for effective, cheap and feasible pharmacologic prophylaxis for PEP has been continued.

Phospholipase A₂ is presumed to play a pivotal role in the inflammatory cascade associated with acute pancreatitis^[8]. This has been the basis for several prospective placebo-controlled randomized controlled trials (RCTs) evaluating non-steroidal anti-inflammatory drugs (NSAIDs), potent inhibitors of phospholipase A₂ activity, in the prevention of PEP. In 2003, Murray *et al*^[9] showed that rectal diclofenac given immediately after ERCP reduced the incidence of PEP in a high-risk patient population. These findings were corroborated by Khoshbaten *et al*^[10], who also demonstrated that immediate administration of rectal diclofenac after ERCP reduced the incidence of acute pancreatitis in patients undergoing pancreatogram. Studies evaluating rectal indomethacin have also suggested a protective effect against PEP in patients undergoing pancreatography or ERCP for biliary obstruction^[11,12]. In spite of these promising findings, the relatively small sample size of each of these studies and the heterogeneous study groups, have yielded overall inconclusive results.

A meta-analysis published in 2008 attempted to further validate the role of prophylactic rectal NSAIDs on PEP^[13]. Assuming a two-tailed $\alpha = 0.05$, a power of 0.9 and PEP incidences of 12.06% and 4.38% in the placebo and NSAID groups respectively, the authors concluded that a total of 586 patients would be required to demonstrate the intended decrease in the incidence of PEP. By compiling the results of four previous RCTs, an adequate pooled sample size was achieved to detect a statistically significant 64% (95% CI: 0.22-0.60) reduction in acute pancreatitis in patients who received NSAIDs immediately after ERCP when compared to placebo. The results of this meta-analysis further emphasized the apparent benefit of rectal administered NSAIDs for PEP prophylaxis and the need of large prospective multi-center trials to confirm these findings.

On the background of these promising results, Elmunzer *et al*^[14], report the results of a multi-center, randomized, placebo-controlled, double-blind clinical trial conducted to determine the effect of a single dose of rectal indomethacin administered immediately after ERCP in patients at elevated risk for PEP. Inclusion cri-

teria selected patients with an elevated baseline risk of PEP as defined by one or more of the following major criteria: clinical suspicion of sphincter of Oddi dysfunction (SOD), a history of PEP, pancreatic sphincterotomy, precut sphincterotomy, more than eight cannulation attempts, pneumatic dilatation of an intact biliary sphincter, or ampullectomy. Patients were also eligible if they met two or more of the following minor criteria: an age of less than 50 years and female sex, history of recurrent pancreatitis (≥ 2 episodes), three or more injections of contrast agent into the pancreatic duct with at least one injection to the tail of the pancreas, excessive injection of contrast agent into the pancreatic duct resulting in opacification of pancreatic acini, or the acquisition of a cytologic specimen from the pancreatic duct with the use of a brush. The study design consisted of patients randomly assigned to receive either two 50 mg indomethacin suppositories or two identical-appearing placebo suppositories immediately after ERCP. The randomization was concealed by using centralized location and stratified by study center. The primary and secondary outcomes of the study were the development of PEP^[15] and moderate or severe PEP, respectively. Patients with post-ERCP abdominal pain were hospitalized, followed clinically, and had their serum amylase and lipase measured at least once 24 h after the procedure. Patients discharged after uneventful ERCP were contacted within 5 d and again at 30 d to capture delayed occurrence of primary outcome and to assess for any delayed adverse events.

The study enrolled a total of 602 subjects from February 2009 through July 2011. An interim analysis recommended the study to be terminated early on the basis of the benefit of indomethacin compared with placebo. A total of 295 patients received indomethacin, and 307 patients received placebo. Baseline characteristics were similar in the two study groups. The majority of patients (82%) had a clinical suspicion of sphincter of Oddi dysfunction. The overall incidence of PEP was 13.1% (79 of 602 patients). The incidence of PEP was 9.2% (27 of 295 patients) in the indomethacin group compared to 16.9% (52 of 307) in the placebo group ($P = 0.005$), corresponding to an absolute risk reduction of 7.7 percentage points, relative risk reduction of 46%, with a number needed to treat to prevent one additional episode of PEP of 13. The secondary outcome of moderate or severe PEP occurred in 40 patients, 13 (4.4%) in the indomethacin group compared to 27 (8.8%) in the placebo group ($P = 0.03$). Among patients hospitalized for PEP, the median length of hospital stay was 0.5 d shorter in the indomethacin group (3.5 d) than in the placebo group (4 d) ($P < 0.001$). A persistent protective effect of indomethacin against PEP was noted in the post-hoc analysis of patients stratified based on their pre-treatment risk of PEP^[16], regardless of whether patients had undergone pancreatic stenting, clinical suspicion of SOD, and in all subtypes of SOD. The authors concluded that among patients at high risk for post-ERCP pancreatitis, rectal indomethacin significantly reduced the incidence of the

condition.

Acute pancreatitis remains the most common major complication of ERCP. NSAIDs represent an attractive pharmacological agent for PEP prophylaxis because they are inexpensive, can be easily administered and have a relatively low risk profile. Previous efforts to endorse NSAIDs for PEP prophylaxis have been limited by small single-center studies with conflicting results.

This study by Elmunzer *et al.*^[14] is the first large multi-center, randomized, controlled trial that demonstrates the protective effects of a single dose rectal indomethacin against PEP in high-risk patients. The validity of the conclusions is supported by a number of the study methodological strengths including double blinded randomized design, adequate allocation concealment, strict clinically meaningful definition of PEP, thorough follow up with very low lost-to-follow-up rate and intention-to-treat analysis. The authors should also be commended for following the patients thirty days post-procedure to evaluate for any delayed pancreatitis or adverse events. A reduction in the incidence of PEP with rectal NSAIDs in the study group consisting primarily of patients with clinical suspicion of SOD (82%) confirms the benefit of this prophylactic agent in this challenging patient population. This finding is congruent with previous trials suggesting a maximal benefit from prophylactic NSAIDs in high-risk patients. Moreover, this study showed that the relative treatment effect of indomethacin remained across the spectrum of patient's risk of PEP. These results, in conjunction with a trend toward benefit with respect to rates of PEP in patients without clinical suspicion of SOD treated with indomethacin, suggest the need of additional studies to confirm a potential protective effect even in low-risk patients. The very high prevalence of patients with suspected SOD in this trial should be considered when interpreting the external validity of the results and applying them to other high risk PEP patients.

Prophylactic temporary pancreatic duct stenting has been widely accepted for PEP prophylaxis^[17]. One of the main limitations of previous prospective trials regarding the effects of NSAIDs for PEP prophylaxis is their failure to report the use of prophylactic pancreatic stents in their study population. A particular strength of this study is that the majority of patients (> 80%) underwent pancreatic stent placement in addition to the study intervention (indomethacin or placebo). Indomethacin reduced the risk of PEP to a similar degree irrespective to whether the patient received a pancreatic stent or not. These findings highlight the additive protective effect of NSAIDs for PEP prophylaxis in high-risk patients receiving temporary pancreatic duct stenting. Furthermore, it suggests that NSAIDs may be an alternate non-invasive prophylactic measure for PEP in those patients in whom pancreatic stenting may not be feasible or not recommended; however, this requires further investigation.

Elmunzer *et al.*^[14] also reported that prophylactic indomethacin was associated with decreased severity of PEP, which is congruent with previous findings by

Sotoudehmanesh and colleagues. In the subgroup of patients that were hospitalized post-ERCP, the indomethacin group also had a shorter hospital stay when compared to placebo. These results suggest that the benefits of NSAIDs are not limited to reducing the incidence of PEP; but potentially also includes disease severity modulation presumably by regulating the inflammatory response and clinical manifestation of PEP. If further validated, these findings have both clinical as well as economic implications, given the substantial morbidity with increasing severity of PEP and associated health care expenditures.

In summary, this multi-center double blinded randomized controlled trial further supports the use of prophylactic rectal NSAIDs in the prevention of PEP and addresses several limitations of previous studies that have been met with general skepticism. This study demonstrates that rectal indomethacin can reduce the incidence and severity of PEP in high-risk population consisting mostly of patients with suspected SOD and could potentially have a benefit even in low-risk patients. The low cost and risk profile associated with a single standard dose of rectal indomethacin makes this an attractive prophylactic pharmacological agent in those patients in whom this medication is not otherwise contraindicated. While clinical judgment in selecting patients with appropriate indications for ERCP remains the most important measure in preventing PEP, rectal indomethacin is a safe, easily administered, widely available pharmacological prophylactic measure that could change how we address this serious ERCP-associated complication.

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