Dig Dis Sci (2015) 60:2863–2864
DOI 10.1007/s10620-015-3746-1

EDITORIAL

Chemoprevention of Post-ERCP Pancreatitis with Rectal NSAIDs: Does Poking Both Ends Justify the Means?

Tilak Shah[1] · Alvin Zfass[1] · Mitchell L. Schubert[1]

Received: 2 June 2015 / Accepted: 4 June 2015 / Published online: 23 June 2015

Acute pancreatitis, the most common severe complication of endoscopic retrograde cholangiopancreatography (ERCP), accounts for up to 50 % of all ERCP-related lawsuits. The overall incidence of post-ERCP pancreatitis (PEP) is 1.6–15 % [1]. Yet, the likelihood of developing this complication is several-fold higher in patients with risk factors such as female gender, pre-cut papillotomy, endoscopic sphincterotomy, suspected sphincter of Oddi dysfunction, and previous PEP [2]. In patients with multiple risk factors, the incidence of pancreatitis after ERCP may be as high as 30–40 % [1].

Preventing PEP has been an area of intense investigation. A number of interventions have been studied for their potential to reduce PEP, but most have failed to reproducibly demonstrate efficacy in randomized controlled trials. Based on current evidence, guidelines from Europe and the USA support two therapeutic interventions to reduce PEP: prophylactic pancreatic stent and rectal nonsteroidal anti-inflammatory drugs (NSAIDs) [3, 4]. Pancreatic stenting reduces the absolute risk of developing PEP by 10–13 % in high-risk patients, presumably by preventing mechanical obstruction of the papillary orifice induced by sphincter or Oddi spasm or edema [5].

The rationale behind use of NSAIDs to prevent PEP is their ability to inhibit a number of pathways thought to participate in the pathogenesis of acute pancreatitis, including activation of phospholipase A2, increased prostaglandin synthesis, and neutrophil–endothelial cell attachment. Experimental data supporting the benefits of NSAID therapy in acute pancreatitis along with its low cost and ease of administration have spurred a number of clinical trials. In the largest trial, Elmunzer et al. [6] randomized 602 patients to 100 mg indomethacin as a rectal suppository or a placebo rectal suppository immediately after ERCP. The primary outcome, PEP, was defined based on consensus criteria as new upper abdominal pain, an elevation of pancreatic enzymes to at least three times the upper limit of normal 24 h post-ERCP, and hospitalization for at least two nights. Most patients in this study underwent ERCP for suspected sphincter of Oddi dysfunction, and most received a prophylactic pancreatic stent. PEP occurred in 9.2 % of patients in the rectal indomethacin group versus 16.9 % of patients in the placebo group ($p = 0.005$). Moderate-to-severe pancreatitis developed in 13 patients (4.4 %) in the indomethacin group and in 27 patients (8.8 %) in the placebo group ($p = 0.03$). The number needed to treat (NNT) to prevent one episode of pancreatitis was only 13 patients, consistent with a prior meta-analysis of four randomized controlled trials ($n = 912$) that reported a pooled NNT of 15 [7].

In the current issue of *Digestive Diseases and Sciences*, Lua et al. [8] report a prospective, randomized, open-label study comparing the administration of 100 mg diclofenac as a rectal suppository immediately after ERCP versus no pharmacologic intervention on the incidence of PEP in 144 "high-risk" patients. The diagnosis of PEP was based on the same consensus criteria used by Elmunzer et al. [6] as described above. PEP occurred in seven patients in the diclofenac group (10 %) versus four patients in the control group (5 %) ($p > 0.05$). No patient developed severe PEP. The authors conclude that rectal diclofenac does not reduce the incidence of PEP in high-risk patients.

✉ Tilak Shah
Tilak.Shah@va.gov

[1] Division of Gastroenterology, 111N, Hunter Holmes McGuire Veterans Affairs Medical Center and Virginia Commonwealth University Health System, 1201 Broad Rock Blvd, Richmond, VA 23224, USA

Although the results of the current study appear to contradict the conclusions of the largest randomized trial evaluating the efficacy of NSAIDs in preventing PEP as well as a definitive meta-analysis on this subject, it is not the only randomized trial that has failed to demonstrate reduction in PEP with diclofenac. In the trial by Cheon et al. [9], in which 207 patients were randomized to diclofenac 50 mg or placebo by mouth 30–90 min before and 4–6 h after ERCP, PEP occurred in ~18 % of patients in each group.

Should this study change our current practice? Although the aim and design of this study are laudable, there are a number of caveats. The failure of this study to find a difference between treatments does not necessarily indicate that no difference exists as the a priori power calculation underestimated the number of subjects required. The number was calculated based on a 20 % reduction in the absolute risk of PEP, although prior studies reported only a 6–8 % reduction. Furthermore, the rate of PEP in this study was only 5 %, at least threefold lower than that reported in the literature, especially surprising since the patients did not undergo prophylactic pancreatic stenting, and confirming the observation that the majority of procedures were indicated for conditions associated with a low risk for PEP (e.g., obstructive jaundice, cholangitis, and malignancy). The categorization of "high risk" principally reflected the difficulty "inexperienced" endoscopists had cannulating the desired duct. Finally, the study was unblinded, particularly important since assessment of two of the three consensus criteria for PEP, pain and hospital stay, is subjective and vulnerable to bias.

Although Lua et al. [8] should be commended for undertaking and reporting this study, the insufficient number of subjects, low rate of PEP, and the lack of blinding limit its ability to change clinical practice. Avoiding unnecessary ERCP remains the most effective prophylaxis against PEP. The EPISOD trial provides strong evidence to eschew ERCP for suspected sphincter of Oddi dysfunction type III [10]. In patients with a strong indication for ERCP and a high pre-test probability of developing PEP, the bulk of evidence continues to support a modest, yet clinically significant, beneficial effect for rectal NSAIDs. Nevertheless, several questions remain unanswered. Are indomethacin and diclofenac equally efficacious? Could higher doses of NSAIDs further reduce PEP or merely increase the risk of complications such as renal failure and bleeding? What is most efficacious to prevent PEP: rectal NSAIDs, pancreatic stenting, or a combination of both? Addressing these questions in a randomized, double-blinded fashion has a greater potential to alter and improve clinical care than yet another trial merely assessing the efficacy of rectal NSAIDs.

Conflict of interest None.

References

1. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol*. 2007;102:1781–1788.
2. Chen JJ, Wang XM, Liu XQ, et al. Risk factors for post-ERCP pancreatitis: a systematic review of clinical trials with a large sample size in the past 10 years. *Eur J Med Res*. 2014;19:26.
3. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013;108:1400–1416.
4. Dumonceau JM, Andriulli A, Deviere J, et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy*. 2010;42:503–515.
5. Choudhary A, Bechtold ML, Arif M, et al. Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review. *Gastrointest Endosc*. 2011;73:275–282.
6. Elmunzer BJ, Scheiman JM, Lehman JA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med*. 2012;366:1414–1422.
7. Elmunzer BJ, Waljee AK, Elta GH, et al. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. *Gut*. 2008;57:1262–1267.
8. Lua GW, Muthukaruppan R, Menon J. Can rectal diclofenac prevent post endoscopic retrograde cholangiopancreatography pancreatitis? *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-015-3609-9.
9. Cheon YK, Cho KB, Watkins JL, et al. Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. *Gastrointest Endosc*. 2007;66:1126–1132.
10. Cotton PB, Durkalski V, Romagnuolo J, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. *JAMA*. 2014;311:2101–2109.