REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Should we administer rectal anti-inflammatory drugs in all ERCPs in order to prevent pancreatitis? At least, it does not harm!

Authors:
Jesús García-Cano, Miriam Viñuelas Chicano

DOI: 10.17235/reed.2020.6871/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
García-Cano Jesús, Viñuelas Chicano Miriam. Should we administer rectal anti-inflammatory drugs in all ERCPs in order to prevent pancreatitis? At least, it does not harm!. Rev Esp Enferm Dig 2020. doi: 10.17235/reed.2020.6871/2020.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Accepted Article

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

ED 6871 inglés

Should we administer rectal anti-inflammatory drugs in all ERCPs in order to prevent pancreatitis? At least, it does not harm!

Jesús García-Cano and Miriam Viñuelas Chicano

Department of Digestive Diseases. Hospital Virgen de la Luz. Cuenca, Spain

Acute pancreatitis is the most common complication of endoscopic retrograde cholangio-pancreatography (ERCP). The sensitivity of the pancreas, which may respond with such violence to the slightest pressure exerted at the entrance to its main duct in the papilla of Vater, is even philosophically surprising. In fact, each touch on the papilla increases the potential for pancreatitis development. The initial stimulus resulting in obstruction of pancreatic secretion may be the edema caused by the catheter's physical contact, the thermal effect of sphincterotomy, or the overdistension induced by the injected contrast. The triggering fact is followed by a release of inflammatory cytokines, which induce changes in pancreatic microcirculation.

This complication has been thoroughly investigated as millions of therapeutic ERCPs have been carried out worldwide since 1973, and thousands or ERCP-related pancreatitis have consequently ensued.

Traditionally, four categories of factors have been involved in the development of this complication. These have been dubbed the four “Ps”: Patient, Procedure, Pancreatic stents, and drug Prophylaxis.

Clearly defined risk factors for post-ERCP pancreatitis include female gender, history of pancreatitis with or without prior ERCPs, and suspected sphincter of Oddi dysfunction. Other patient-related factors that may likely increase pancreatitis risk include age younger than 35 years (1), non-dilated extrahepatic biliary tract, normal bilirubin levels, and chronic renal failure. Patients with chronic pancreatitis have a lower risk for post-ERCP pancreatitis.

Accepted Article

Regarding the procedure, clearly defined risk factors include difficult cannulation, guidewire passage into the pancreas more than once, and pancreatic contrast injection. An easy way of defining difficult cannulation is the 5-5-2 criterion. Attempts at cannulation for 5 minutes, or 5 attempts where the sphincterotome clearly touched the papilla of Vater, or 2 guidewire cannulations of the main pancreatic duct (2).

Other procedure-related factors that may likely increase pancreatitis risk include precut using a needle-knife papillotome, pancreatic sphincterotomy, sphincteroplasty without prior sphincterotomy, and inability to remove all stones in choledocholithiasis, perhaps due to an increase in maneuvers that may damage the papilla. Intraductal ultrasound during ERCP seems to be a factor for increased likelihood of pancreatitis, but the technique is not widely spread. Whether this risk may be extrapolated to cholangioscopy remains unknown.

When the guidewire enters the pancreas during attempts at common bile duct cannulation, placement of a plastic pancreatic stent is always advisable to prevent pancreatitis (3). The stent should be at least 5 French in order to provide satisfactory drainage. A short stent without inner flaps will most likely be spontaneously expelled, thus obviating the need for another endoscopy to remove it (Fig. 1). Attempting pancreatic cannulation for stent placement alone may be hazardous. For instance, in case of endoscopic ampullectomy, repeated attempts at pancreatic duct cannulation over a surface that is inflamed by prior resection may result in perforation.

As regards drug prophylaxis, a wide variety of drugs have been studied: statins, allopurinol, protease inhibitors, nitroglycerin, somatostatin, epinephrine irrigation of the papilla of Vater, etc. However, the only two therapies shown to clearly reduce post-ERCP pancreatitis rates are aggressive hydration with lactated Ringer's solution (4) and non-steroidal anti-inflammatory drugs (NSAIDs), specifically rectal indomethacin or diclofenac (5).

The protective action of NSAIDs is seemingly associated with the inhibition of phospholipase A2, cyclooxygenase, and other substances that may trigger or perpetuate the inflammatory cascade in pancreatitis.

One of the debates concerning the rectal administration of NSAIDs in ERCP is whether all patients or only those at high risk because of their characteristics or procedural

Accepted Article

complexity will benefit from this approach.

In this issue of *The Spanish Journal of Gastroenterology*, Lindo et al. (6), in a study carried out at Hospital Universitario de La Princesa, a reference university medical center in Madrid, found no decrease in post-ERCP acute pancreatitis rate after the rectal administration of 100 mg indomethacin before each procedure. The study group was made up of 524 consecutive, unselected patients, of which 393 (75%) had a moderate risk. ERCPs were performed over a period of 30 months. Acute pancreatitis developed in 12/277 (4.33%) patients who received the anti-inflammatory drug, *versus* 10/247 (4.04%) in the group without indomethacin.

Similarly, in a previous study that was also reported in this journal, del Olmo et al. (7) found no protective effects of rectal 100 mg diclofenac on post-ERCP pancreatitis. They analyzed 1,512 ERCP procedures performed over a period of seven years and a half. A pancreatitis rate of 3.4% was seen in the diclofenac group *versus* 2.8% in the group without anti-inflammatory drug ($p = 0.554$). Risk factors were present in only 26.1% of patients, similar to the study by Lindo et al. (6).

The studies by Lindo et al. (6) and del Olmo et al. (7) add to prior research where rectal NSAIDs fail to be effective in protecting from pancreatitis when consecutive patient series are analyzed. In these two studies, in both groups (with and without NSAID), a significant proportion of patients had already undergone sphincterotomy, which usually facilitates common bile duct cannulation. Of the four “Ps” associated with post-ERCP pancreatitis development, difficult cannulation often represents a most relevant risk factor.

This is also a criticism made against the study by Levenic et al. (8), who included in their study patients with prior biliary sphincterotomy at a rate of 31.8% (143/449). Therefore, a valid conclusion seems difficult to draw when easy cannulation is already anticipated for a significant proportion of ERCPs, thus eliminating a relevant risk factor.

Patai et al. (9) observed that the protective effect of a suppository 100 mg indomethacin given within 1 hour before ERCP was greater in the group of patients with difficult cannulation. The more complex the cannulation procedure, the greater was the protective effect of indomethacin. Thus, for instance, when precut was

Accepted Article

required following usual attempts at cannulation, post-ERCP pancreatitis rate was 13.8% in the non-NSAID group *versus* 6.7% in the NSAID group (p = 0.007).

Therefore, the question is whether rectal anti-inflammatory drugs should be administered before all ERCP procedures, regardless of the foreseen difficulty level. In the absence of contraindications, the answer today should likely be that it is advisable. In our experience the simplest of ERCPs, such as replacement of a plastic biliary stent, may in seconds turn into a very complex procedure, with significant trauma to the papilla, even when a sphincterotomy had been previously done. Peak blood levels of rectal anti-inflammatory drugs are reached within 30 to 90 minutes after administration, and the drug should be already circulating when the procedure begins.

In fact, the European Society of Gastrointestinal Endoscopy (ESGE) recommends (10) that 100 mg of rectal diclofenac or indomethacin be routinely administered immediately before ERCP to all patients without contraindications for NSAIDs. This is because, besides reducing pancreatitis rates, these drugs also reduce pancreatitis severity and, according to a meta-analysis, even pancreatitis-related mortality (11).

NSAIDs in ERCP are contraindicated in pregnant women prior to gestation week 30, and in patients having suffered from Stevens-Johnson or Lyell syndrome after exposure to anti-inflammatory drugs. The latter contraindication also involves their first-degree relatives. In patients with renal failure, particularly in those on antihypertensive drugs, potential benefits should be assessed on an individual basis. Sphincterotomy bleeding risk does not increase with the rectal administration of 100 mg indomethacin or diclofenac.

The ESGE reserves aggressive hydration with lactated Ringer's solution for patients where NSAIDs are contraindicated and hydric overload can be tolerated. Ringer's solution administration may be stopped should a plastic pancreatic stent be easily inserted during ERCP. When neither NSAIDs nor Ringer's lactate solution can be used, sublingual nitrates are recommended before ERCP (10).

Rectal drug administration via suppositories seems old fashioned and may surprise patients. Rectal indomethacin or diclofenac were not available until very recently in many of our hospitals, and had to be purchased from pharmacies. These drugs have also been used intravenously (12), but only rectal dosing is effective for prophylaxis.

Accepted Article

Hopefully, other options as straightforward as rectal anti-inflammatory drugs will soon be available for the prevention of post-ERCP pancreatitis, as this administration route is certainly highly inelegant!

REFERENCES

1. El Nakeeb A, El Hanafy E, Salah T, et al. Post-endoscopic retrograde cholangiopancreatography pancreatitis: Risk factors and predictors of severity. World J Gastrointest Endosc 2016;8:709-15.

2. Haraldsson E, Kylänpää L, Grönroos J, et al. Macroscopic appearance of the major duodenal papilla influences bile duct cannulation: a prospective multicenter study by the Scandinavian Association for Digestive Endoscopy Study Group for ERCP. Gastrointest Endosc 2019;90:957-63. DOI: 10.1016/j.gie.2019.07.014

3. García-Cano J, Viñuelas Chicano M, Del Moral Martínez M, et al. Pancreatic stent insertion after an unintentional guidewire cannulation of the pancreatic duct during ERCP. Rev Esp Enferm Dig 2018;110:416-20. DOI: 10.17235/reed.2018.5230/2017

4. Wu D, Wan J, Xia L, et al. The efficiency of aggressive hydration with lactated Ringer solution for the prevention of Post-ERCP pancreatitis: A Systematic Review and Meta-analysis. J Clin Gastroenterol 2017;51:e68-e76. DOI: 10.1097/MCG.0000000000000856

5. Patai Á, Solymosi N, Mohácsi L, et al. Indomethacin and diclofenac in the prevention of post-ERCP pancreatitis: a systematic review and meta-analysis of prospective controlled trials. Gastrointest Endosc 2017;85:1144-1156.e1. DOI: 10.1016/j.gie.2017.01.033

6. Lindo Ricce M, Rodríguez López-Salazar T, Mendoza Jiménez-Ridruejo J, et al. Effectiveness of rectal indomethacin in the prevention of acute pancreatitis after endoscopic retrograde cholangiopancreatography in unselected patients. Rev Esp Enferm Dig 2020 [in press].

7. Del Olmo Martínez L, Velayos Jiménez B, Almaraz Gómez A. Rectal diclofenac does not prevent post-ERCP pancreatitis in consecutive high-risk and low-risk patients. Rev Esp Enferm Dig 2018,110:505-9. DOI: 10.17235/reed.2018.5259/2017

Accepted Article

8. Levenick JM, Gordon SR, Fadden LL, et al. Rectal indomethacin does not prevent Post-ERCP pancreatitis in consecutive patients. Gastroenterology 2016;150:911-7. DOI: 10.1053/j.gastro.2015.12.040

9. Patai Á, Solymosi N, Patai ÁV. Effect of rectal indomethacin for preventing post-ERCP pancreatitis depends on difficulties of cannulation: results from a randomized study with sequential biliary intubation. J Clin Gastroenterol 2015;49:429-37. DOI: 10.1097/MCG.0000000000000168

10. Dumonceau JM, Kapral C, Aabakken L, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2019 Dec 20. DOI: 10.1055/a-1075-4080.

11. Yaghoobi M, Alzahrani MA, McNabb-Baltar J, et al. Rectal indomethacin prevents moderate to severe post-ERCP pancreatitis and death and should be used before the procedure: A meta-analysis of aggregate subgroup data. J Can Assoc Gastroenterol 2018;1:67-75. DOI: 10.1093/jcag/gwy006

12. García-Cano J, Reyes Guevara AK, Martínez Pérez T, L. et al. Prevention of post-ERCP acute pancreatitis with intravenous diclofenac administered after the endoscopic intervention [Spanish]. Rev Esp Enferm Dig 2013;105(Supl. I):106.

Accepted Article

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

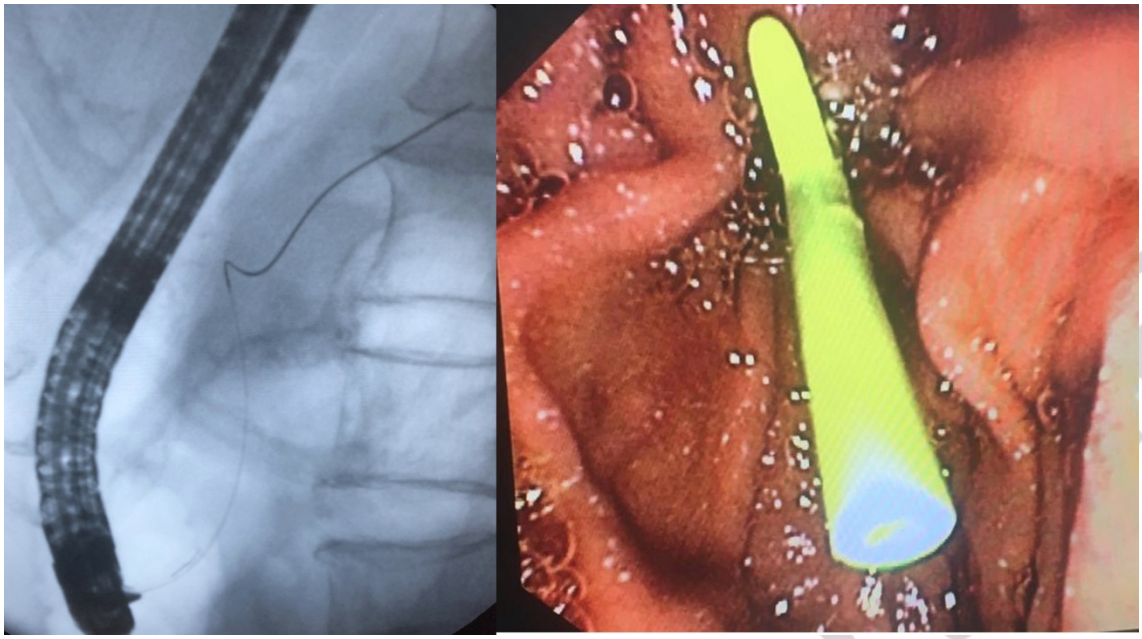

Figure 1. During ERCP, when the guidewire has entered the main pancreatic duct, it is advisable that a 5-French plastic stent be inserted in order to prevent post-ERCP pancreatitis.

Accepted Article