

# Indomethacin prevents post-ERCP pancreatitis in selected high-risk patients

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## Background

Pancreatitis is one of the major complications of cholangiopancreatography (ERCP). It occurs in 1–10 % of patients but the incidence may reach 25 % in high-risk patient populations. Generally post-ERCP pancreatitis (PEP) is mild, but moderate or severe pancreatitis (pancreas necrosis, pseudocyst formation, need of surgical intervention, long hospitalization) may arise in 0.5 % of cases [1, 2].

The most common risk factors for this complication are both patient-related and procedure-related: younger age, female gender, prior ERCP-induced pancreatitis, sphincter of Oddi dysfunction, pancreas divisum, difficulty of cannulation, biliary sphincterotomy or pancreatic opacification [3]. Although some randomized clinical trials (RCTs) have shown a potential benefit of gabexate mesilate and somatostatin in preventing post-ERCP pancreatitis, there are few data to recommend the use of these drugs; moreover, they require continuous infusion and are quite expensive [4, 5].

A few RCTs have demonstrated a potential role of nonsteroidal anti-inflammatory drugs (NSAIDs) as prevention for post-ERCP pancreatitis, but before introducing these prophylactic strategies in clinical practice, more studies are needed [6, 7].

## Summary

Elmunzer et al. conducted a multicenter, randomized, placebo-controlled, double-blind clinical trial comparing the use of a single dose of rectal indomethacin versus placebo for the prevention of post-ERCP pancreatitis in high-risk patients. Patients were considered eligible, if they met at least one major criteria: (clinical suspicion of sphincter of Oddi dysfunction, a history of PEP, pancreatic sphincterectomy, precut sphincterectomy, more than eight cannulation attempts, pneumatic dilatation of an intact biliary sphincter or ampullectomy) or two or more minor criteria (age less than 50 and female gender, a history of recurrent pancreatitis, three or more injections of contrast agent into the pancreatic duct, excessive injection of contrast agent resulting in opacification of pancreatic acini, or the acquisition of a cytologic specimen from the pancreatic duct using a brush). The main exclusion criteria were: active pancreatitis, contraindication to the use of NSAIDs (creatinine level >1.4 mg per deciliter, or active peptic ulcer disease), pre-existing therapy with NSAIDs (except for cardioprotective aspirin), and low risk of post procedure pancreatitis (chronic calcific pancreatitis, biliary stent exchange). After ERCP had been performed, a total of 602 patients were randomized to receive either 100 mg of rectal indomethacin or a placebo immediately after the procedure. The primary outcome was the development of PEP defined as new-onset upper abdominal pain associated with an elevation of pancreatic enzymes  $\geq 3$  URL, and hospitalization for at least two nights. The secondary outcome was the development of moderate or severe post-ERCP pancreatitis. Patients who were discharged after an uneventful procedure were contacted by telephone after 5 days, and again after 30 days to assess for delayed adverse events, and to determine the severity of post-ERCP

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pancreatitis. Adverse events were defined as gastrointestinal bleeding, perforation, infection, renal failure, allergic reaction, myocardial infarction, cerebrovascular accident and death.

The primary outcome occurred in 27 (9.2 %) of 295 patients in the indomethacin group as compared with 52 (16.9 %) of 307 in the placebo group ( $P = 0.005$ ) with an absolute risk reduction of 7.7 %, a relative risk reduction of 46 % and a number needed to treat of 13. A total of 40 patients developed moderate or severe pancreatitis: 13 (4.4 %) in the indomethacin group and 27 (8.8 %) in the placebo group ( $P = 0.03$ ). The benefit of indomethacin on the primary outcome was further evidenced in pre-specified and post hoc subgroups analyses. Adverse events occurred in a small number of patients, and they were not statistically different between the two groups.

### Strengths of the study

- It deals with a clinically relevant problem. ERCP is a common procedure, and pancreatitis is a relatively frequent and potentially life-threatening complication.
- The prophylactic use of a single dose of indomethacin is a low-cost intervention, which may provide a great benefit assuring a very small risk of side effects.
- There were no patients lost to follow-up.

### Weaknesses of the study

- The trial was stopped early because of the net benefit of the NSAIDs prophylaxis. This may have overestimated the treatment effect [8].
- Patients comorbidities and procedure indication are not reported in any detail. This may interfere with the external validity of the study, as the population enrolled may be selected with bias.

### Question marks

- The majority of patients underwent the procedure as an outpatient; this may have reduced the external validity of the study, and the assessment of the primary outcome. Moreover, more than 80 % of the patients had a clinical suspicion of sphincter of Oddi dysfunction (SOD), which is a functional disorder diagnosed using elusive criteria; this may reduce the applicability of the study results to a different population.

- The patient's enrollment was determined after the procedure by the endoscopist, who was allowed to exclude patients considered at low risk of PEP, even if they met one or more inclusion criteria. This may have led to selection bias.
- It would have been interesting to know the confidence intervals of the data to allow a more tailored applicability of the results to different population.

### Sponsorship

Not reported.

### Clinical bottomline

The use of rectal indomethacin is effective in preventing post-ERCP pancreatitis, and in reducing its severity in selected high-risk patients. Since the low incidence of adverse effects after a single dose of NSAIDs, the routine use of this prophylaxis should be considered in clinical practice; more studies are also needed to assess the benefit of indomethacin in populations with different characteristics.

**Conflict of interest** None.

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