

# Should we incorporate topical epinephrine in the ESGE guideline on prevention of post-ERCP pancreatitis?



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Pancreatitis remains the most frequent and lethal adverse event (AE) that may follow endoscopic retrograde cholangiopancreatography (ERCP). Fortunately, it is also the only AE for which significant advances have been made. Since 2010, four scientific societies have issued guidelines about the prophylaxis of post-ERCP pancreatitis (PEP). All of them have recommended rectal nonsteroidal anti-inflammatory drugs (NSAIDs) as the cornerstone of pharmacological prophylaxis of PEP (► **Table 1**).

This has led to slow adoption in the community: In 10 years, the proportion of endoscopists who use rectal NSAIDs for PEP prophylaxis has increased from 15% to 54% to 98% [1–4]. The latest survey reported use of rectal NSAIDs by 98% of pancreaticobiliary endoscopists but by only 40% of them in average-risk patients [4]. This is despite the demonstration of NSAID effica-

cy in this risk category of patients by 11 of 14 meta-analyses published to date [5]. Reasons accounting for this slow and incomplete adoption include disbelief and confusion because scientific societies recommend NSAIDs in different risk categories of patients (► **Table 1**). Surprisingly, cost could become another reason: a single NSAID suppository costs \$ 347 in the United States, and it is billed between \$ 50 and \$ 5000 to ambulatory patients by Californian hospitals [6]. Therefore, exploration for alternatives that might be even more widely available, easy to use, innocuous, and cheap than NSAIDs is welcome.

In the current issue of *Endoscopy International Open*, a meta-analysis suggests that spraying epinephrine onto the papilla is effective to prevent PEP [7]. Overall, the meta-analysis found no significant difference between PEP rates in patients

► **Table 1** Recommendations from Scientific Societies about pharmacological prophylaxis of post-ERCP pancreatitis.

Society, date	First-line prophylaxis	Target population	Timing
European Society of Gastrointestinal Endoscopy, 2010 [18]	Rectal NSAIDs	All patients	Pre-ERCP [5]
American Society of Gastrointestinal Endoscopy, 2017 [9]	Rectal NSAIDs	High-risk patients	Pre- or post-ERCP
Japanese Society of Gastroenterology, 2017 [10]	Rectal NSAIDs	NR	Pre- or post-ERCP
Chinese Societies Consortium <sup>1</sup> , 2019 [11]	Rectal NSAIDs/somatostatin (minimum 11 hours)	High-risk patients	Pre-ERCP if patient-related risk factors are present; post-ERCP if only procedure-related risk factors are present

ERCP, endoscopic retrograde cholangiopancreatography; NR, not reported; NSAIDs, non-steroidal anti-inflammatory drugs

<sup>1</sup> Chinese Digestive Endoscopist Committee, Chinese Endoscopist Association, Chinese Physicians' Association, Pancreatic Disease Committee, Chinese Physicians' Association

who received topical epinephrine or not (relative risk [RR], 0.63; 95% confidence interval [CI], 0.32–1.24). Because some of the studies included in the meta-analysis also used rectal indomethacin for PEP prophylaxis, the authors performed a subgroup analysis that excluded such studies. In this subgroup, topical epinephrine was associated with a lower risk of PEP compared with no topical epinephrine or placebo (RR, 0.32; 95% CI, 0.18–0.57). Hence, the authors suggest considering topical epinephrine for PEP prophylaxis in the case of rectal NSAIDs unavailability or if there is any contraindication to their use.

In 2013, a network meta-analysis identified topical epinephrine as the most efficacious prophylaxis for PEP [8]. However, epinephrine was not retained in any of the four subsequent guidelines from large Endoscopy Societies on this topic [5, 9–11]. That is because the network meta-analysis included only two randomized controlled trials (RCTs); furthermore, these excluded (!) therapeutic ERCP and used a non-standard definition of PEP [12, 13]. The only new data since 2013 consist of a RCT published in abstract form with no information about the type of ERCP (diagnostic or therapeutic) and the definition of PEP [14]. Two low-quality case-control studies published in 2001 and 2009 have been included in the current meta-analysis. One, again, excluded therapeutic ERCP and the other one was restricted to patients who had balloon sphincteroplasty [15, 16].

The authors suggest using topical epinephrine as a replacement for rectal NSAIDs in patients with “absolute contraindications to NSAIDs such as allergies to NSAIDs, end-stage kidney disease, or patients who have had proctocolectomy”. End-stage renal disease is an important concern as it may be a risk factor for PEP [17]. Patients undergoing chronic dialysis can receive a single dose of NSAIDs without concerns. Other patients should not receive topical epinephrine of dubious efficacy and be deprived from effective alternatives such as high-volume hydration with lactated Ringer’s solution, sublingual glyceryl trinitrate, infusion of somatostatin for 11 hours or prophylactic pancreatic stenting [5]. We also think that rather than using topical epinephrine if rectal indomethacin is unavailable, solutions should be found to make rectal indomethacin or diclofenac available or alternatives with proven efficacy should be used.

In conclusion, the current meta-analysis could stimulate further research on topical epinephrine in placebo-controlled RCTs of therapeutic ERCP, in combination with effective regimens different from rectal NSAIDs. However, it does not support a change in current recommendations from the ESGE. If rectal NSAIDs are contraindicated, which is truly exceptional, several alternatives are effective. Until now, that has not been demonstrated for topical epinephrine.

### Competing interests

The authors declare that they have no conflict of interest.

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