



# Prevention of post-ERCP pancreatitis: where are we now?

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## Abstract

Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is a first-line therapeutic investigation to manage a wide range of pancreatic and biliary disorders. Post-ERCP pancreatitis is a well-recognised common complication with significant morbidity and mortality. There are a large number of interventions that have been employed to decrease this risk. In this mini-review, we summarise measures that can be used to decrease the risk of post ERCP pancreatitis. Procedural factors that will be explored include patient selection, cannulation time, pancreatic duct injection of contrast, pre-cut sphincterotomy and guide-wire assisted cannulation. Therapeutic interventions that will be covered include rectal NSAIDs, aggressive pre-hydration of Ringer's lactate and prophylactic pancreatic stents.

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## Introduction

Endoscopic Retrograde Cholangio Pancreaticography (ERCP) is used worldwide and is a first line therapeutic procedure to manage a range of pancreatic and biliary disorders. As with many endoscopic procedures, ERCP has potential complications associated with it, of which Post-ERCP Pancreatitis (PEP) is the most common. The reported incidence of PEP is up to 10% in unselected cases and carries significant morbidity [1]. Risk factors for PEP include female gender, sphincter of oddi dysfunction and a prior history of PEP [2]. Table 1 summarises the main risk factors for PEP.

ERCP is practised as a therapeutic test in the vast majority of situations, with MRCP and EUS providing less invasive diagnostic modalities. It is vital to limit the occurrence of PEP and a variety of measures have been employed. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), prophylactic pancreatic stenting

and specific procedural-related factors are the best proven interventions to decrease the incidence of PEP. This review will explore these various interventions and summarise the available evidence in relation to their effectiveness in reducing PEP in an evolving field.

## NSAIDs

Multiple studies have shown that there is a clear benefit of using rectal NSAIDs to reduce the risk of PEP. Sajid et al. [3] performed a systematic review of thirteen randomised controlled trials and demonstrated that rectal NSAIDs significantly reduced the risk of PEP in all-risk patients by 57% (OR 0.43). This is echoed in a meta-analysis performed by Yaghoobi et al. [4] (OR 0.49) and Sun et al. [5] (RR 0.45). However, all the evidence is not positive: A large randomised controlled trial by Levenick et al. [6] suggested that the incidence of PEP was not reduced by rectal NSAIDs in average and low-risk patients, adding to the



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controversy. Subsequent meta-analyses have looked at studies performed in low- to average-risk of PEP have shown a benefit [7,8] and this may mean that the Levenick study could be an outlier. Another smaller study performed by Rainio et al. in 2017 [9] revealed that diclofenac had no beneficial effect in reducing PEP in unselected patients, but the authors do suggest this could be due to their low incidence of PEP. The evidence in the UK has been sparse, with only one RCT in 2003 demonstrating its benefit [10]. A more recent retrospective observational study has demonstrated benefit in a district general hospital and has provided further evidence of its benefit [11]. Phospholipase A2 has been implicated in the pathogenesis of acute pancreatitis and found to be significantly elevated in severe pancreatitis [12]. Both indomethacin and diclofenac are potent inhibitors of phospholipase A2 suggesting a mechanistic rationale for its use [13]. An observational study performed in the UK revealed that those patients already on NSAIDs for other medical conditions may have a protective effect on developing complications related to acute pancreatitis [14], although there has been no study to date looking at a direct relationship between using NSAIDs in the acute setting and the prevention of complications related to acute pancreatitis. There have been very few studies examining the efficacy of NSAIDs in reducing the severity of established PEP. A meta-analysis performed by Elmunzer et al in 2008 showed that rectal NSAIDs reduces the severity [15] but this was not supported by a more recent meta-analysis performed by Li et al. [16].

There have been limited studies comparing different NSAIDs, with most of the meta-analyses comparing all NSAIDs with placebo, where a clear benefit has been demonstrated. Mohamed Alizadeh et al performed a small randomised study of 372 patients and found that rectal indomethacin and diclofenac were more effective than naproxen [17]. Sajid et al's meta-analysis suggests that diclofenac is more effective than indomethacin [3], with a 55% reduction in PEP with diclofenac compared to 41% with indomethacin.

Despite the negative studies, the low cost of NSAIDs, ease of use, the growing body of evidence and safety profile contribute to the recommendation by the American Society of Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) that rectal NSAIDs should be given peri-procedure in all without contraindication.

### Procedural factors

There are a number of procedural factors that have been linked to the development of PEP but randomised trials are difficult because of confounding factors. Funatsu et al. [18] performed an observational, retrospective analysis of 1334 patient who underwent ERCP over four years (all performed by experienced endoscopists) and found that a higher risk of PEP was likely in those with longer cannulation times (specified as more than fifteen minutes), especially if there is a history of previous PEP. There were limitations to this study, namely the fact it was a single-centre study and not all patient-related risk factors were accounted for, e.g. Sphincter of Oddi dysfunction. Similarly, longer cannulation time is a surrogate marker of a difficult ERCP and not something that can be controlled. Testoni et al. [19] report a prospective multi-centre study from 2010 which reviewed 3635 ERCPs performed in a mixture of low- and high-volume centres in an attempt to determine if volume was related to complications. Interestingly, the rates of PEP did not differ significantly between the types of centre nor between expert and non-expert operators. They identified multiple at-

tempts to cannulate the ampulla, pancreatic duct cannulation, injection of contrast into the pancreatic ductal system and pancreatic sphincterotomy as significant associations with PEP. The conclusion was that these are independent risk factors for PEP, regardless of the expertise of the endoscopist, These risk factors are also identified in multiple other studies internationally (e.g. Bailey et al [20]).

Table 2 summaries the variety of procedural techniques that have been assessed in their ability to reduce PEP. Tse et al. [21] performed a meta-analysis in 2012 examining the effects of Guide-Wire (GW) assisted cannulation as opposed to contrast-guided. It was found that GW improved the cannulation success rate (RR 1.07) and reduced the need for a pre-cut sphincterotomy (RR 0.75), suggesting both independently reduces the rate of PEP. Tse et al. also found that the GW-assisted technique reduced the rate of inadvertent pancreatic duct manipulation (either contrast injection or cannulation), although this was non-significant (RR 0.88). However, if a pancreatic duct stent was used, the use of GW compared with contrast-assisted did not significantly reduce the rate of PEP (4.8% v 5.5%, RR 0.92). Artifonet al [22] performed an RCT of 300 patients to assess the use of GW-assisted cannulation and the results support Tse's meta-analysis (OR 0.43).

Precut sphincterotomy and fistulotomy have been suggested to be linked to increased rates of PEP but it is likely that these are surrogate markers for difficult cannulations and prolonged procedures rather than increasing the rate per se. There is evidence that early use of precut does not increase rates of PEP and some studies have demonstrated that it can significantly reduce the rate of PEP, as demonstrated by a retrospective, comparative study by Ang et al. [23]. In cases of difficult biliary cannulation, the use of precut sphincterotomy in place of persistence of other techniques has been shown to reduce the risk of PEP [24,25].

### Prophylactic pancreatic stents

Use of prophylactic pancreatic stents to reduce PEP has been examined extensively in the literature.

Choudhary et al. [26] performed a meta-analysis of the utility of pancreatic stents in reducing PEP. Despite the heterogeneity in the studies, particularly the size and type of stent, it did show a significant benefit of using stents to reduce PEP (OR 0.22). This has been supported by further meta-analyses performed by Mazeki et al [27] and Singh et al. [28]. An analysis performed by Das et al. [29] found them to be cost-effective in reducing the rates of PEP. It is particularly effective in patients who undergo pancreatic guide-wire cannulation or contrast injection to achieve biliary cannulation. ARCT comparing pancreatic guide wire cannulation with other precut techniques revealed significantly higher rates of PEP [30] in the double guide wire technique. The 2014 ESGE guidelines [31] advocate the restricted use of pancreatic guide wire cannulation for biliary cannulation only in situations where the pancreatic duct is inadvertently cannulated. Pancreatic stenting is useful in those patients with Sphincter of Oddi dysfunction, a known risk factor for PEP, as demonstrated by Saad et al. (OR 4.1) [32]. A large multi-centre trial demonstrated that prophylactic pancreatic stenting in high risk patients may lessen the severity of pancreatitis, although this conclusion was derived from the fact that the majority of patients that did develop PEP were mild [33]. A small retrospective, observational study did show there may be some benefit in reducing PEP by giving rectal NSAIDs if a prophylactic pancre-

atic stent has failed [34]. A network meta-analysis performed by Akbar et al. [35] suggests that rectal NSAIDs may be superior to pancreatic duct stents to reduce PEP, although it was limited by the small number of studies included. This supports a post-hoc analysis performed by Elmunzer et al. [36] which also suggested that those who received rectal NSAIDs alone were at the lowest risk of PEP compared to NSAIDs plus pancreatic stent. Larger, prospective clinical trials comparing these methods are required in order to conclude as to whether one is more effective than the other in reducing PEP.

There are very few studies assessing which calibre of stent is more effective. Lee et al. [37] performed a small study of 101 patients and demonstrated that a 3F pancreatic stent in patients with difficult biliary cannulation is effective and safe in patients to reduce PEP. Expert opinion suggests that a long 3-4F or short 5-6F stents may reduce the risk of stent migration, which may cause delayed-onset PEP [38].

### Pre-hydration

There have been few studies examining the effect of intensive fluid hydration to patients undergoing ERCP to prevent PEP. A systematic review performed by Smeets et al. [39] did support the use of aggressive hydration but the majority of studies were small and generally observational, and the authors do highlight that larger studies examining this specific effect were required before guidance could be given. As to the type of fluid that should be given, the American College of Gastroenterology guidelines [1] advocate the use of Ringer's lactate solution based on one small study [40]. A more recent large study performed by Park et al. [41] did show a significant decrease in PEP when patients with aggressive hydration pre-procedure in average to high-risk patients. The evidence based for this is currently limited and more studies are required to demonstrate a benefit of this. There have currently been no head-to-head trials between pre-hydration and NSAIDs and Smeets's meta-analysis note that as none of the studies included NSAIDs, a conclusion regarding any additive effect could not be made.

### Conclusion

(Table 3 summarises the various interventions that have been explored and the guidance associated with the evidence.)

PEP carries a significant morbidity and a mortality. There are multiple cost-effective interventions demonstrated to reduce the risk of PEP including peri procedural NSAIDs and prophylactic pancreatic stenting. Interestingly the combined use does not seem to reduce the risk of PEP further although large blinded studies are awaited. The precise role of pancreatic stents in the prevention of PEP is unclear in the era of NSAIDs but should be considered when the pancreatic duct has been cannulated or contrast injected. It would not seem logical to cannulate a virgin pancreatic duct to place a stent especially if NSAIDs are used. The growing body of evidence, ease of use and safety profile of rectal NSAIDs peri-procedure clearly supports their use unless contraindicated. The type of NSAID and timing of administration requires further studies. Identifying those patients at higher risk of PEP may help to determining which of these interventions should be used or identify a subgroup requiring both NSAIDs and stenting. Rectal NSAIDs and prophylactic pancreatic stenting if the pancreatic duct has been manipulated should be used in all without contraindication. There is limited evidence for aggressive pre-hydration but this has not been proven in subsequent studies. Further studies could focus on the best com-

ination of methods to prevent PEP. Case selection for ERCP is beyond the remit of this mini-review but it is clear that the most efficient method of avoiding PEP is not to perform an ERCP and necessity need to be questioned for all procedures.

### Tables

**Table 1:** Risk factors for PEP.

Patient-related factors	Procedure-related factors
Female gender	Difficult cannulation
Sphincter of Oddi dysfunction	Cannulation or injection into the pancreatic duct
Prior history of PEP	Biliary balloon sphincter dilation
Younger age	
Normal serum bilirubin	

Adapted from: Dumonceau JM, Andriulli A, Elmunzer BJ et al. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) guideline – updated June 2014. *Endoscopy*. 2014; 46: 799-815.

**Table 2:** Techniques that could be used to help reduce PEP.

Guide wire-assisted biliary cannulation
Early pre-cut sphincterotomy
Prophylactic pancreatic stents
Short-wire technique
Double-wire technique (if performed with the use of a prophylactic pancreatic stent)

Adapted from: Elmunzer BJ. Reducing the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Digestive Endoscopy*. 2017; 29: 749-757.

**Table 3:** Interventions with evidence of reducing PEP.

Evidence available	Limited evidence
Rectal NSAIDs	Pre-procedural aggressive hydration
Prophylactic pancreatic stenting	
Guidewire-assisted biliary cannulation	
Early pre-cut sphincterotomy	

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