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EDITORIAL

A closer look at universal prophylactic rectal NSAIDs in prevention of post-ERCP pancreatitis

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Post-ERCP (endoscopic retrograde cholangiopancreatography) pancreatitis (PEP) is the most common complication seen in 4% to 10% of patients undergoing ERCP, which may go up to 15% in high-risk patients without any prophylaxis with a mortality of around 0.7% [1, 2]. Freeman et al. in a landmark paper identified the risk factors associated with PEP as shown in Table 1. A patient is considered to be at high risk if one definite or two likely patient-or procedure-related risk factors are present [3-6].

Since long, there have been efforts to minimize the risk of PEP or to reduce the severity of PEP. Simultaneously, there was development in imaging such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS), both of which do not fiddle with the papilla of Vater and thus avoid PEP. With the judicious use of these diagnostic modalities, a lot of diagnostic ERCPs can be avoided. Thus, the first step in the prevention of PEP is to avoid all sorts of diagnostic ERCP. PEP is also dependent on the expertize of the endoscopist. In the high-risk group, ERCP should preferably be started by experts and in patients, where technical difficulties arise during the procedure, an expert should take over earlier.

Various pharmacological and endoscopic measures have been tried to avoid PEP. Of these, a few have stood the test of time and have become a part of general standard operating procedure (SOP) and part of guidelines of various societies. It is important for all who do ERCP to understand and know about their status in day-to-day practice.

The first and best known of these modalities is the use of prophylactic pancreatic duct (PD) stenting in the high-risk group. The rationale for this lies in understanding that edema at the papilla leading to obstruction to the flow of pancreatic juice is responsible for PEP. Since mid-90s, multiple studies have studied prophylactic PD stenting to reduce the incidence of PEP. The endoscopic measures taken to prevent PEP must be individualized and governed by patient risk factors, technical factors encountered during the procedure, risk of adverse events associated with stenting, endoscopist expertize and preference. Recent meta-analyses of randomized controlled clinical trials (RCTs) have shown a significant reduction in PEP and also showed a significant reduction in the severity of PEP with PD stenting (odds ratio [OR], 0.32; 95% CI, 0.23–0.45; $p < 0.001$). PD stent placement reduced the risk of PEP by 65% compared with no PD stents. PD stent placement was also associated with reduced occurrence of both moderate (OR, 0.38; 95% CI, 0.23–0.63) and severe (OR, 0.20; 95% CI, 0.06–0.65) PEP [7-11]. Prophylactic PD stenting in preventing PEP has been recommended in recent guidelines by the American Society of Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) [12, 13]. Prophylactic PD stenting is reserved for cases, where PD is inadvertently cannulated. PD stenting requires special skill set and may not be always easy. Failed PD stenting in high-risk patients may pose bigger problems. It is advised not to make special efforts to cannulate the PD for stenting, but to do that only if PD is getting inadvertently cannulated.

Pharmacological interventions to prevent PEP are simpler and easy to use. Multiple drugs have been tried, but non-steroidal anti-inflammatory drugs (NSAIDs) are the current proven favorite. Landmark study by Elmunzer et al. in 2012 demonstrated the effectiveness of rectal NSAIDs in preventing PEP [14], following that there have been many RCTs showing its effectiveness. Rectally administered NSAIDs, half an hour before starting procedure, are first-line pharmacologic prophylaxis for preventing PEP today. There have been many points of discussion, i.e. route of administration, indomethacin or diclofenac and the timing of insertion of suppository (before, during and after). Most of these issues are now well settled. One hundred milligrams of indomethacin or diclofenac suppository inserted before starting the procedure is the standard of care today and recommended by all international professional societies.

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Table 1 Risk factors associated with PEP

Risk factors	Patient related	Procedure related
Definite risk factors	Female sex Suspicion of SOD Previous pancreatitis Previous PEP	Difficult cannulation > 1 PD cannulation Pancreatic injection
Likely risk factors	Younger age Non-dilated biliary duct Normal serum bilirubin Absence of chronic pancreatitis End-stage renal disease	Precut or pancreatic sphincterotomy Balloon sphincteroplasty Failure to complete stone clearance

PEP post-ERCP pancreatitis, *SOD* sphincter of Oddi dysfunction, *PD* pancreatic duct

For some time, there has been a debate as to its effectiveness only in high risk or all patients undergoing ERCP. Both ASGE and ESGE guidelines [12, 13] have beautifully illustrated and summarized that there was a significant reduction in PEP with universal administration of rectal NSAIDs in patients undergoing ERCP, irrespective of risk status. This was the conclusion drawn by the systematic review and meta-analysis of 11 studies by Yu et al. (2018) and a multicentre, single-blinded RCT of 2600 patients undergoing ERCP in China by Luo et al. (2016) that the pre-procedural administration of rectal indomethacin in unselected patients in comparison to the risk-stratified post-procedural group reduced the risk of PEP [15, 16]. Same has been the matter of a recent study done by Agarwal et al. [17] published in this issue of the *Journal,* in which they performed a retrospective analysis of a prospectively maintained database of all 769 patients, who had undergone ERCP from January 2018 till March 2020 at All India Institute of Medical Sciences (AIIMS), New Delhi. Thirty-four patients (4.4%) developed PEP, a majority of which were mild 29 (85.3%). This study concluded that routine use of prophylactic NSAIDs effectively prevents the occurrence of PEP in unselected consecutive patients ($p < 0.001$). This strategy of prophylactic pre-ERCP administration of rectal indomethacin in all patients is superior to the strategy of purposeful rectal indomethacin given after ERCP in only high-risk patients to reduce the risk of PEP [17-19]. All studies are of the conclusion that rectal NSAIDs are simpler, more effective and safe in the prevention of PEP in populations with all levels of risk. Data from India, definitely helps us in applying the same to our population.

Simultaneous to the use of drugs, data on use of aggressive fluid therapy in preventing PEP has emerged. It is based on the understanding that the mechanism behind pancreatitis is disturbed micro-circulation and hemodynamic dysfunction, which is manifested as a rise in blood urea nitrogen (BUN) and hematocrit pointing to a state of volume depletion. This logic was utilized by aggressive intravenous (IV) fluid administration for the prevention of PEP. A large volume or "aggressive" intravenous hydration (usually defined as lactate ringer solution bolus of 20 mL/kg peri-procedural, followed by 3 mL/kg/h for 8 hours) was effective for reducing the risk of PEP [12, 20-22]. However, in clinical practice, the use of this strategy may be limited because it requires inpatient hospitalization for administering the total volume of fluid. Thus, it may not be feasible for outpatient department (OPD) patients. In addition, some patients may be at increased risk for developing fluid overload, for instance patients with cardiac or kidney disease. In a meta-analysis of 12 trials, including 3524 patients undergoing ERCP, aggressive intravenous hydration resulted in a lower risk of PEP compared with standard-volume hydration (OR, 0.47; 95% CI, 0.34–0.66) [12]. No significant differences in adverse events was observed between the two groups. A meta-analysis of nine RCTs by Radadiya et al. that included 2094 patients concluded that aggressive hydration with lactated ringer decreases the incidence of PEP by 56% compared to standard hydration. In addition, it decreases the length of hospitalization by one day, with no significant difference in fluid overload complications [23]. Finally, aggressive hydration therapy is to be given to all high-risk patients unless there is a risk of fluid overload except in those in whom a prophylactic PD stent is deployed. Though the optimal regimen is uncertain, current available data support IV hydration as a preventive strategy.

The effectiveness of the above modalities has evoked interest in research workers to see whether there is any benefit or not of combining more than one modality. A combination of NSAIDs and aggressive hydration in comparison to either of the two has shown a lower OR of PEP in two of the meta-analysis [24, 25]. The result of the FLUYT RCT dispelled this idea done across 22 Dutch hospitals that enrolled 826 patients with moderate to high-risk PEP, randomized to receive either rectal NSAID alone or in combination with aggressive fluid therapy and found that hydration does not diminish PEP rates by a clinically significant amount in people already receiving NSAID prophylaxis, but showed a trend towards less severe PEP [26]. Combining rectal NSAIDs with prophylactic PD stenting in comparison to either approach alone added no benefit in preventing PEP as per meta-analysis by Akbar et al. [11]. Recent RCT by Sotoudehmanesh

et al. failed to demonstrate non-inferiority or inferiority of pharmacological prophylaxis alone (rectal indomethacin, intravenous hydration with Ringer's lactate) compared with PD stenting plus pharmacological prophylaxis in the prevention of PEP in high-risk patient (12.6%, 95% CI 8.6 –17.6%) vs. 33 (15.9%, 95% CI 11.4 –21.4%) [27]. But this was a small trial not adequately powered to draw conclusions. So, whether combinations of preventative measures perform better than single interventions or not, it is yet to find acceptance. A routine combination of rectal NSAIDs with other measures is not recommended by the latest guidelines by ASGE and ESGE societies [12, 13].

With the current understanding, one will recommend the universal use of prophylactic NSAIDs suppository 30 minutes prior to the procedure. Though the evidence may be lacking, in case of repeated non-intended cannulation of PD, prophylactic stenting in this select group is advisable, even if they have received prophylactic NSAID suppository. This study also provides evidence supporting the efficacy of routine use of prophylactic rectal NSAIDs to prevent the occurrence of PEP in unselected consecutive patients in a real-world scenario without increasing any adverse effect of the drug. It has also been included in the ESGE (2020) guidelines and recently added to the latest ASGE (2023) guidelines.

Declarations

Conflict of interest AK and PS declare that they have no conflict of interest.

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