Indomethacin prevents post-ERCP pancreatitis: the addition of topical epinephrine to indomethacin does not improve benefit

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We read with interest this recent randomized control trial from Kamal *et al.* in the *American Journal of Gastroenterology* (1). They compared topical epinephrine spray applied to the papilla along with rectal indomethacin to rectal indomethacin alone in high-risk patients and found no significant difference in rates of post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis (PEP) (6.7% *vs.* 6.4%). There were no differences in rates of moderate to severe PEP.

Several methods have been examined to reduce the risk of post-ERCP pancreatitis including improved patient selection, procedural techniques including different cannulation strategies and pancreatic duct (PD) stents, as well as topical and systemic pharmacological prophylaxis (2).

Different cannulation techniques have been studied and found to reduce the risk of PEP including wire-guided cannulation (3), physician controlled wire guided cannulation (4), and early-needle knife sphincterotomy (5). Insertion of PD stents has been shown to reduce the risk of PEP in high-risk patients and the risk of severe and necrotizing PEP (6). However, stent placement may have drawbacks, which include failed placement in up to 5–10% of patients in experienced centers, migration, and ductal perforation (7). Thus, the use of PD stents is limited to patients with an increased risk of moderate to severe pancreatitis and appears not additive to the use of rectal indomethacin in recent studies.

Multiple systemic pharmacologic agents including calcium channel blockers (8), nitrates (9), somatostatin analogs (10) and inflammatory agents have been studied to prevent the inflammatory cascade in post-ERCP pancreatitis, but known had shown promise until non-steroid inflammatory drugs (NSAIDs), in particular rectal indomethacin (11). In 2012 Elmunzer *et al.* published a landmark multicenter randomized trial comparing one dose of rectal indomethacin to placebo post-ERCP in high-risk individuals (12). It found that 9.2% of patients in the indomethacin group developed PEP compared to 16.9% in the placebo group, a statistically significant difference. Indomethacin also decreased the rate of moderate-to-severe pancreatitis, 4.4% to 8.8% in the placebo group. However, the majority of patients in this study had possible sphincter of Oddi dysfunction, a clinical entity where the benefit of ERCP is unclear and there is an elevated risk of PEP. Additionally, the majority (80%) of patients also had a pancreatic duct stent placed so it is unclear if it was the combined effect of indomethacin and the pancreatic duct stent that improved outcomes.

A recent randomized controlled trial involving 449 mainly average risk patients failed to find a benefit with rectal indomethacin administration when compared to placebo (13). However, 30% of patients in that study were considered high-risk and it was in a single center. However, a large multicenter randomized control trial in China showed significant reduction of PEP and moderate to severe PEP with routine pre-procedural administration of rectal indomethacin to all patients when compared to post-procedural administration of indomethacin to

high-risk patients (14). This study only included patients with a native papilla. Additionally, a large retrospective cohort study involving 4,017 patients from our group included low-risk patients undergoing ERCP (15). We demonstrated that rectal-indomethacin reduced the odds of PEP by 65% and moderate to severe pancreatitis by 83%. Based on these studied the European Society for Gastrointestinal Endoscopy (ESGE) has recommended the usage of rectal indomethacin before or after ERCP in all patients undergoing ERCP, while the American Society for Gastrointestinal Endoscopy recommends usage in all high-risk patients and suggests usage in average-risk patients (16,17).

Aggressive hydration with lactated ringers has been studied as potential PEP prophylaxis. Buxbaum *et al.* conducted a pilot study in 62 patients comparing hydration to aggressive lactated ringers hydration post-procedure and found that 17% of patients in the standard hydration group developed PEP compared to no patients in the aggressive hydration group, a statistically significant difference (18). A larger follow-up randomized controlled trial (RCT) by Choi *et al.* compared aggressive hydration before, during and after the procedure to standard hydration following the procedure in 510 patients with a native papilla in three tertiary referral centers in Korea (19). They found that aggressive hydration significantly reduced the rates of PEP from 9.8% to 4.3% as well as the rate of moderate to severe pancreatitis. However given that the vast majority of ERCPs are performed in the ambulatory or outpatient setting, an 8 to 10 hours regimen is not felt to be feasible for the majority of patients undergoing ERCP and even for high-risk patients, which limits its applicability in clinical practice (20). Furthermore, rectal indomethacin was not administered in any of these studies, so it is unclear if LR offers additional benefit.

Various topical agents have been studied for PEP prophylaxis. They involve topically spraying various pharmaceutical agents on the papilla prior to cannulation. A prior study by our group failed to show benefit for topical lidocaine, which has been shown to reduce cholecystokinin release and inhibit sphincter of Oddi spasm (21). Topical epinephrine was been studied as it causes arteriolar vasoconstriction and reduces papillary edema and transient pancreatic duct obstruction similar to pancreatic duct stents (22). Indeed, prior small single-center studies as well as a network meta-analysis had shown that topical epinephrine reduced the risk of PEP.

However, the multi-national multi-center randomized control trial by Kamal *et al.* failed to find any risk reduction with topical epinephrine when rectal indomethacin was used in high-risk patients. There are several potential reasons for these seemingly discordant results. First, rectal indomethacin has a systemic effect on multiple pathways both in pancreatic acinar tissue, vasculature and the immune system, which may reduce inflammation and could reduce the transient benefit of topical epinephrine (23). Indeed, mice studies have found that topical epinephrine's effect only lasts for 1–5 minutes (24). Another potential reason for the lack of efficacy in this study is that multiple mechanisms contribute to PEP; transient pancreatic duct obstruction, papillary edema, chemical and thermal injury from radiocontrast in the pancreatic duct, and guidewire-associated trauma to the pancreatic duct (25). While topical epinephrine may address the role of papillary edema temporarily it does not address these other mechanisms. Thus, it is possible that a subgroup such as patients with only difficult cannulation may benefit while other subgroups are unlikely to have benefit. Finally, it is important to note that endoscopic techniques in practice and clinical trials vary substantially creating heterogeneity limiting the utility of meta-analysis, including the meta-analysis that demonstrated significant benefit with topical epinephrine.

In conclusion, routine usage of rectal indomethacin is warranted in all patients, as is consideration of concomitant pancreatic duct stents in high-risk patients. Usage of aggressive hydration can be considered but it is unclear if offers incremental benefit when rectal indomethacin is used. Topical therapies such as topical epinephrine have not shown benefit in reducing PEP and this study by Kamal *et al.* demonstrates that it does not offer additional benefit when used with rectal indomethacin in high-risk patients, but may offer benefit in certain subgroups, which have yet to be defined.

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