Editorial Commentary

Usefulness of post-endoscopic retrograde cholangiopancreatography pancreatitis prevention by high dose rectal indomethacin

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Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is a serious adverse event of ERCP. The incidence of PEP is high: 3.8–15.1% (1-3). Various factors can complicate the development of PEP, such as impaired pancreatic fluid outflow, elevated pressure in the pancreatic duct, and damage to the pancreatic duct caused by ERCP. Consequently, the pancreatic acinar cells are impaired; also, trypsin activation and hypercytokinemia are triggered (4). Guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) and the European Society for Gastrointestinal Endoscopy (ESGE) state that young age, female gender, and suspected sphincter of Oddi dysfunction (SOD) are all definite "patient-related risk factors" for PEP (5,6). By contrast, along with pre-cut sphincterotomy, pancreatic injection and difficult cannulation are specifically identified in the guidelines as "procedure-related risk factors" for PEP (5,6). Many investigations and reports have indicated various measures to avoid PEP. They include pancreatic duct stenting after ERCP (7), and administration of nonionic iodide radiographic contrast medium (8), nonsteroidal anti-inflammatory drugs (NSAIDs) (9-11), and NSAIDs with nitrates (12). Among these, the administration of NSAIDs has received wide attention. Several randomized controlled trials (RCTs) and meta-analyses have assessed the use of NSAIDs with rectal dosage of 50–100 mg. Actually, NSAIDs reportedly play an important role in the development of acute pancreatitis (13,14) while serving as potent inhibitors of neutrophil endothelial interactions, cyclooxygenase, and phospholipase A2. Rectal administration of indomethacin according to ESGE guidelines, immediately before and after ERCP, can prevent PEP from developing in patients without contraindication (5).

One report (9) described a controlled RCT that included comparison of the effects of 100 mg of rectal indomethacin used to treat 82 patients at high risk for PEP and the effects of 2.6 g suppository of glycerin used to treat an 84-patient placebo group at high risk for PEP without pancreatic stent placement. The PEP incidence rate was 20.2% (17/84) in the placebo group (P=0.01), but only 4.9% (4/82) in the rectal indomethacin group (9). One study was a double-blind, randomized, placebo-controlled RCT executed at multiple centers to assess rectal indomethacin effects on 602 patients who were at high risk for PEP. The rate of PEP incidence was 16.9% for the placebo patients (P=0.005) but was only 9.2% for the patients who received indomethacin (10). These trials' results indicate that rectal indomethacin might decrease PEP incidence in patients at high risk for PEP. Furthermore, Serrano *et al.* (15) reported results of a meta-analysis of 21 RCTs, indicating lower risk of PEP in an NSAID group [risk difference (RD): −0.05; 95% confidence interval (CI): −0.07 to −0.03; number needed to treat (NNT), 20; P<0.05].

Reports of the literature have also described optimal timing of rectal administration of NSAIDs. One study examined preprocedural administration of 100 mg rectal indomethacin to 1,297 patients (preprocedural group) to prevent PEP. Those results were compared to those obtained

from post-procedural administration of 100 mg rectal indomethacin to 1,303 patients of a post-procedural group who were at high risk. The preprocedural group rate of PEP incidence was 4%; that of the post-procedural group was 8% in (P<0.0001). This study demonstrated the benefit of administering rectal indomethacin before ERCP to prevent PEP (11). As presented above, earlier reports have described that rectal indomethacin 100 mg can reduce the incidence of PEP in patients at high risk. Moreover, several reports have described studies that have found the optimal dose of rectal administration of diclofenac. No difference was found in the incidence of PEP between patients who were administered 25 and 50 mg rectal diclofenac (9% *vs.* 0%, respectively; not significant, P=0.101) (16). After Yoshihara *et al.* compared doses of 50 and 25 mg rectal diclofenac to prevent PEP, they reported that the incidence of PEP in the 50 mg group was significantly lower than that in the 25 mg group (15% *vs.* 33%, respectively; P=0.018) (17). As those results imply, the optimal dose remains unclear.

In 2020, Fogel *et al.* (18) reported no advantage derived from increasing rectal indomethacin to 200 mg compared to the standard 100 mg regimen for patients at high risk for PEP. In all, 1,037 patients at high risk for PEP were included in the study. They were assigned randomly to receive indomethacin of a standard dose (100 mg, n=515) or indomethacin of a high dose (200 mg, n=522). Results revealed PEP in 141 (14%) of 1,037 patients. Results also showed that, of 515 patients, 76 (15%) had PEP in the standard-dose indomethacin group. Of 522 patients, 65 (12%) had PEP in the high-dose indomethacin group [risk ratio (RR) 1.19, 95% CI: 0.87–1.61; P=0.32]. No significant difference was found between the two groups in PEP, but severe adverse events of kidney injury and transient ischemic attack occurred in the high-dose indomethacin group only. Based on results of this study, we infer that escalation to the high-dose of rectal indomethacin confers no advantage over the standard 100 mg regimen. Moreover, we infer that current practices should be continued unchanged. Further studies must be undertaken to elucidate the pharmacokinetics of rectal NSAIDs such as indomethacin and diclofenac and to ascertain the optimal timing of their administration to prevent PEP.

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