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ORIGINAL ARTICLE

EFFICACY OF PER RECTAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS TO PREVENT POST ENDOSCOPIC RETROGRADE CHOLANGIOPANCREA-TOGRAPHY PANCREATITIS: A COMPARATIVE STUDY

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Abstract:

Background and aims: *Acute pancreatitis is the most common major post-ERCP complication ranging as high as 10% to 40%. Rectal NSAIDS (Indomethacin or Diclofenac) seem to be the most promising drugs to prevent post ERCP pancreatitis. We performed a trial to investigate the efficacy of indomethacin or diclofenac.* ***Methods:*** *A prospective randomized comparative trial was performed at Dhaka from January 2013 to June 2019. Patients undergoing ERCP were randomly selected to group-A and group-B. Diclofenac 50mg suppository was given to group-A patients and Indomethacin 100mg suppository was given to group-B patients during or just after ERCP. The primary outcome was acute pancreatitis following the procedure which was defined by new upper abdominal pain, elevation of pancreatic lipase to at least 3 times the upper limit of normal level 24 hours after ERCP and hospitalization for 02 nights. Retrospective analysis of data of 122 patients who had undergone ERCP in 2012 but had no history of rectal NSAIDS (group C) was done.* ***Results:*** *Total 613 patients were included in this study and followed up. Post ERCP pancreatitis developed in 21(8.5%) patients of group-A (n=247), in 19(7.78%) patients of group-B (n=244) and in 20(17.85%) patients of group-C (n=122)(p=0.02). Moderate to severe pancreatitis was found in 08(3.23%) patients of group-A, in 06(2.45%) patients of group-B and in 12(9.83%) patients of group-C(p= 0.01). Administration of these NSAIDS showed clear benefit to reduce occurrence of Post ERCP pancreatitis when compared with no drug group (P=0.01). The efficacy of indomethacin compared with diclofenac was similar (P=0.874).* ***Conclusions:*** *Prophylactic use of rectal indomethacin or diclofenac during or just after ERCP significantly reduces the incidence of post ERCP pancreatitis. These NSAIDs are inexpensive, safe and should be used routinely in each patient undergoing ERCP.*

Keywords: *ERCP, NSAIDs, Post ERCP, Pancreatitis*

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Introduction:

Endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted therapeutic modality of the pancreatobiliary tree diseases. It has many complications. Among the complications, acute pancreatitis is the most common. The incidence of this complication is 1–40% when there are high-risk factors.[1] In most of the prospective series, the incidence reported ranged between 3.5% and 20% for non-selected and for high-risk patients, respectively. The risk factors for post-ERCP pancreatitis (PEP) are either patient or procedure-related.[1,2] Eighty to ninety percentages of the episodes of PEP are mild. But a small proportion of patients develop severe pancreatitis, resulting in prolonged hospitalization and increased morbidity and mortality.[3] Despite technical improvements, the incidence of PEP has not yet decreased.[4]

Prevention of PEP is a continuous challenge. The ideal prophylactic agent should be a drug with a low cost, be easily administrated and with mild or no adverse effects. The identification of patients at a high risk of this complication is difficult before the endoscopic procedure because many risk factors are procedure-related. There is no gold standard tool to prevent this complication. To date, pancreatic stent placement is currently recommended by some guidelines.[5,6] However, pancreatic stenting is a difficult procedure to perform; in addition, many endoscopists are not familiar with this procedure.

More than 35 pharmacologic agents have been studied for the prophylaxis of PEP. However, no medication has proven to be effective in preventing PEP and no pharmacological prophylaxis is in widespread clinical use.[7,8,9,10] NSAIDs are potent inhibitors of phospholipase A2, cyclooxygenase and neutrophil–endothelial interactions which are believed to play an important role in the pathogenesis of acute pancreatitis. NSAIDs are inexpensive and easily administered and have a favorable risk profile, making them an attractive option in the prevention of PEP. Preliminary studies evaluating the protective effects of single-dose rectal indomethacin or diclofenac in PEP have been conducted, and suggest a beneficial effect.[11,12] The aim of this study was to evaluate the efficacy of rectally administered NSAIDs in reducing the incidence of PEP in high-risk patients.

Methods:

A prospective randomized comparative trial was performed at gastroenterology department, Sir Salimullah Medical College Mitford Hospital, Dhaka from January 2013 to June 2019. Total 613 patients were included in this study. Patients were eligible if they met one or more of the following criteria: clinical suspicion of sphincter oddi dysfunction (SOD), a history of PEP, pancreatic sphincterotomy, precut sphincterectomy, more than eight cannulation attempts, pneumatic dilatation of an intact biliary sphincter, or ampullectomy. Patients were also eligible for inclusion if they met two or more of the following criteria: age less than 50 years and female sex, a history of recurrent pancreatitis (> two episodes), three or more injections of contrast agent into the pancreatic duct, excessive injection of a contrast agent into the pancreatic duct resulting in opacification of pancreatic acini, or the acquisition of a cytologic specimen from the pancreatic duct with the use of a brush.

The exclusion criteria were: unwillingness to the study, age less than 18 years, pregnancy, breastfeeding mother, standard contraindication for ERCP, hypersensitivity to NSAIDs, previous use of NSAIDs within 1 week, creatinine level ≥1.6 mg/dl, active or recent (4 weeks) gastrointestinal hemorrhage, chronic calcified pancreatitis, pancreatic head malignancy, ERCP for biliary stent removal or exchange without anticipated pancreatogram, subjects with prior biliary sphincterotomy now scheduled for repeat biliary therapy without anticipated pancreatogram and anticipated inability to follow the study protocol.

Eligible patients who provided written informed consent underwent randomization at the conclusion of the ERCP procedure, because patients without risk factors could be included in the study on the basis of procedure-related factors alone. Patients were randomly selected to group-A and group-B. Diclofenac 50mg suppository was given to group-A patients and Indomethacin 100mg suppository was given to group-B patients during or just after ERCP. Retrospective analysis of data of 122 patients who had undergone ERCP in 2012 but had no history of rectal NSAIDs (group C) was done.

The ERCP procedures were performed with the patient under topical pharyngeal anesthesia with 2% lidocaine and after administration of sedation (midazolam) and analgesia (fentanyl) intravenously. Patients received supplemental oxygen (3 to 5 l/min) through a nasal external device and infusion of 200 to 500 ml of 0.9 % saline solution. Pancreatic stents were only used to treat pancreatic fistulas, not to prevent any pancreatitis events in any cases. Immediately after the procedure, patients were randomly assigned to receive either Diclofenac 50mg suppository (group-A) and Indomethacin 100mg suppository (group-B). The suppositories were administered immediately after ERCP while the patient was still in the procedure room.

PEP was considered the main outcome variable. It was defined by the development of new or increased abdominal pain consistent with pancreatitis, and elevated amylase or lipase greater than three times the normal upper limit until 24 hours after the

procedure, and hospitalization for at least 2 nights. The severity was determined according to consensus guidelines, with mild PEP resulting in a hospitalization of <3 days, moderate PEP resulting in a hospitalization of 4–10 days, and severe PEP resulting in a hospitalization of > 10 days or leading to the development of pancreatic necrosis or pseudocyst, or requiring percutaneous or surgical intervention. Asymptomatic hyperamylasemia was defined as any amylase level at least three times above the normal serum level in the absence of abdominal pain, as defined by the consensus criteria.[12]

Patients were kept under surveillance in the endoscopy recovery area for 3 hours after ERCP. Measurement of serum amylase was performed at 2 hours after ERCP in all study patients. Patients who were asymptomatic after 4 to 6 hours of surveillance remained in their assigned bed where clinical surveillance was continued for up to 24 hours. If new abdominal pain suggestive of pancreatic origin appeared at any moment during the surveillance period, the 2-hour amylase level was noted and confirmed with serum lipase determination in the following hours. In addition, all usual laboratory examinations were performed when acute pancreatitis of any etiology was established.

All data were recorded on standardized data-collection forms by an investigator who was unaware of study-group assignments. All data were analyzed subsequently. The descriptive phase of the statistical analysis included the presentations of data as raw values, percentages and mean ± standard deviation. Student's t test was used for continuous variables, and ÷2 or Fisher's exact tests were used for qualitative variables when appropriate. Furthermore, the absolute risk reduction (ARR), relative risk reduction (RRR) and number needed to treat (NNT) were calculated. Results were considered significant when $P < 0.05$. Statistical analysis was conducted using SPSS® version 17 for Windows (SPSS Inc., Chicago, IL, USA).

Results:

Table 1 shows the baseline characteristics of the patients in the groups. No significant differences were found when variables were compared.

During the study period, 613 patients who met the inclusion and exclusion criteria were included. Two hundred and forty seven patients (40.29%) received 50 mg Diclofen (Group-A) and 244 patients received 100 mg indomethacin rectally (Group-B), and 122 patients (19.90%) received no NSAIDs (group-C).

Table-I

Baseline characteristics of patients included in the groups:

Characteristics	Diclofenac group (N = 247)	Indomethacin group (N = 244)	No drug group (N = 122)	P
Female	148(60.00 %)	151 (62.19 %)	86 (70.23 %)	0.273
Male	99 (40.00%)	93 (37.80 %)	36 (29.76 %)	
Age (years)	50.59 ± 17.55	51.58 ± 18.50	54.0 ± 17.85	0.394
Without comorbidity	168	159	78	0.427
Comorbid conditions	79	85	44	
Normal total bilirubinpre-ERCP	80	92	34	0.660
Elevated total bilirubinpre-ERCP	167	152	88	
Previous cholecystectomy	89	85	41	
Dilated bile duct byimaging studies pre-ERCP	168	159	89	0.506
Post-ERCP diagnostics				
Choledocolithiasis	107	108	50	
Begin biliary stenosisand/or leakage	54	52	21	
Suspected sphincter ofOddi dysfunction	36	34	21	
Normal cholangiogramand/or pancreatogram	25	26	16	
Malignant biliary tractStenosis	25	24	14	
Pre-ERCP amylase level (U/L)	56.39 ± 21.52	57.49 ± 22.56	54.36 ± 20.78	0.539

Table II shows the post ERCP outcome. Sixty patients developed PEP, 21 in the Diclofenac group (8.50 %), 19 in the Indomethacin group (7.78 %) and 20 in the no NSAIDs group (16.39 %); this difference was significant (P = 0.014).

Table-II

Post ERCP out come

Group	No complication	Post ERCP Pancreatitis	P
A (247)	226	21 (8.50 %)	0.014
B (244)	225	19 (7.78 %)	
C (122)	102	20 (16.39 %)	
Total	553	60 (9.78 %))	

According to Cotton's classification, the PEP was mild in 34 patients (56.66%) and moderate in 26 patients (43.3 %); of these moderate pancreatitis, there were 12 cases in the no drug group and 8 case in the Diclofenac group and 6 case in the Indomethacin group (P = 0.014), as shown in Fig. 1.

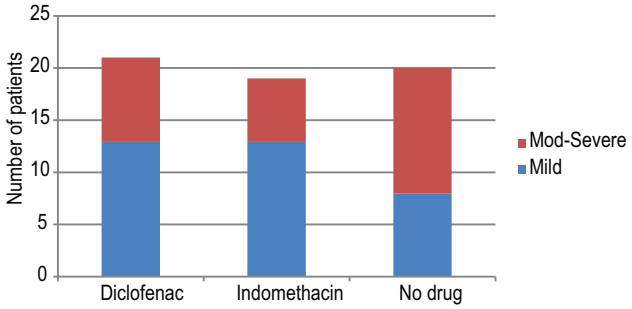

Fig.-1: *Distribution of mild and moderate-severe PEP among groups*

Comparison among the group A, B & C are showed in Table III. This is seen that both the NSAIDs are effective in preventing PEP. P=0.007 in indomethacin group and 0.02 in diclofen group. Comparison between these two drugs is insignificant (P=0.874).

Table-III

Comparison among different groups

Groups	No complication	Mild	Mod-severe	P
Diclofen (Gr-A)	226 (91.49%)	13 (5.263%)	08 (3.238%)	0.874
Indomethacin(B)	225 (92.21%)	13 (5.327%)	06 (2.459%)	
No drug(C)	102 (83.60%)	08 (6.557%)	12 (9.836%)	0.025
Diclofen(A)	226 (92.21%)	13 (5.263%)	08 (3.238%)	
Indomethacin(B)	225 (91.49%)	13 (5.327%)	06 (2.459%)	0.007
No drug(C)	102 (83.60%)	08 (6.557%)	12 (9.836%)	

Table-IV

Patient and procedure-related risk factors identified for the development of PEP

Risk factor	Diclofenac Group (N = 247)	Indomethacin group (N =244)	No drug group (N = 122)	P
Patient-related				
Female sex	148 (60.00 %)	151 (62.19 %)	86 (70.23 %)	0.27
Suspected sphincteroddi dysfunction	36	34	22	0.74
History of recurrent acutePancreatitis	12	13	7	0.77
Previous post-ERCPpancreatitis	6	6	2	0.53
Normal serum bilirubin.	78	75	35	0.63
Procedure-related				
Attempts to cannulation	7.3 ± 3.5	7.2 ± 3.6	7.1 ± 3.5	0.96
Time cannulation	6.3 ± 3.5	6.5 ± 3.5	6.7 ± 3.6	0.16
Difficult cannulation of thebile duct (>8 attempts)	114	112	58	0.87
Failed cannulation of thebile duct	12	12	6	0.58
Precut (access)sphincterotomy	147	143	67	0.51
Biliary sphincterotomy	147	145	70	0.73
Diameter of the bile duct	11.5 ± 5.3	11.6 ± 5.3	11.6 ± 4.2	0.84
Biliary Stent	78	79	32	0.08
Pancreatography	124	123	55	0.34
Number of passes	1.4 ± 0.6	1.4 ± 0.5	1.5 ± 0.6	0.25
Number of injections	1.5 ± 0.6	1.5 ± 0.7	1.6 ± 0.4	0.52
Pancreatography extension				
* Partial	26	26	12	0.14
* Full	98	97	43	
Pancreatic sphincterotomy	21	20	8	0.36
Pancreatic stenting	6	6	3	0.62
Total procedure time	23.2 ± 6.7	23.2 ± 6.7	24.6 ± 7.3	0.21

Risk factors for PEP are described in Table IV. They were distributed similarly in both groups with no significant differences. In addition, no differences in the distribution of sex or age were observed. No significant differences were observed when analyzing the development of complications in patients older and younger than 50 years (P=0.44).There was no difference in the distribution of a history of previous cholecystectomy (P = 0.12).

The comparison between groups that developed and did not develop PEP is described in Table V.

Forty nine cases of pancreatitis occurred in females and 11 cases in males (P = 0.14).The mean age of the 60 patients with PEP was 48.3 ± 16.2 years, lower than the mean age of 53.6 ± 18.4 years for the 553 patients without pancreatitis; however, the difference was not significant (P = 0.21). The length of hospital stay for those patients who suffered mild pancreatitis was 2.7 ± 0.95 days and 3.8 ± 1.3 days for moderate pancreatitis (P = 0.14). There was no mortality as a result of PEP. At 2 hours after ERCP, the mean serum amylase was 141.9 ± 92.6 U/l in the diclofenac group, 141.9 ± 92.6 U/l in the indomethacin group and 216.5 ± 105.2 U/l in the no drug group (P < 0.001). In patients who developed pancreatitis, the mean serum amylase at 2 hours after ERCP was 1187.6 ± 789.3 U/l and a mean serum lipase level of 5052.6 ± 2805.1 U/l was measured in the first 24 hours after ERCP.

Table-V

Comparison between groups with and without PEP

Characteristics	Patients with post ERCP pancreatitis (N = 60)	Patients without post ERCP pancreatitis (N = 553)	P
Female	49	336	0.14
Male	11	217	
Age (years)	48.3 ± 16.3	53.7 ± 18.1	0.21
<50 years	31	240	0.44
>50 years	29	313	
Dilated bile duct by imaging studies pre ERCP	40	384	0.58
Without dilation bile duct by imaging studies pre ERCP	20	169	
Diameter of the bile duct by ERCP (mm)	9.0 ± 2.1	11.9 ± 5.0	0.001
With previous cholecystectomy	37	263	0.12
Without previous cholecystectomy	23	290	
Elevated pre-ERCP bilirubin	51	378	0.12
Normal pre-ERCP bilirubin	9	175	
Number of attempts to cannulate the biliary tract	9.1 ± 2.7	7.1 ± 3.5	0.02
Difficult cannulation			
<8 attempts	14	316	0.005
>8 attempts	46	237	
Precut (access) sphincterotomy			
Yes	49	297	0.01
No	11	256	
Biliary sphincterotomy			
Yes	31	328	0.54
No	29	225	
Cannulation time of the bile duct (min)	8.7 ± 2.8	6.1 ± 3.5	0.001
ERCP Length (min)	30.0 ± 3.7	23.7 ± 7.2	0.001
Pancreatography			
Yes	49	236	0.002
No	11	317	
Pancreatography extension			
Serum amylase at 2 hours post-ERCP (U/L)	1163.5 ± 999.6	176.9 ± 105.2	0.001

However, we observed significant differences in several outcome results such as the number of attempts to cannulate the bile duct, in the performance of precut sphincterotomy, the time to cannulate the bile duct and the total duration of the procedure (P = 0.001), as well as if patients required pancreatography, also in the number of attempts to pass guide wires and in the injection of contrast material into the pancreatic duct. There was no difference in the extension of pancreatography (P = 0.39). Two patients in each group required pancreatic stenting because pancreatic fistulas were diagnosed during ERCP (P = 0.62).

Discussion:

ERCP has become an important therapeutic modality for pancreatic and biliary diseases. Acute pancreatitis is the most common complication of ERCP. Other complications include hemorrhage, perforation, cholangitis and cholecystitis.[13,14,15,16]

The overall incidence of PEP in our study was 9.78 %, which is comparable to that reported in other series. The frequency of PEP was higher in females (49 females versus 11 males) (Table-I). This finding is also consistent with those of other prospective studies.[15,16,17,18,19]Our results found that the use of rectally administered diclofenac or indomethacin compared with no drug decreased the incidence of PEP in patients at a risk of developing this complication as showed in Table 2 (8.50, 7.78 % versus 16.39 %), and the difference was significant (P = 0.014). The clinical and statistical significance of the intervention was expressed by an ARR of 0.15 (15 %), RRR of 0.75 (75 %) and a NNT of 6.5 patients to prevent one episode of pancreatitis. The efficacy of indomethacin compared with diclofenac was similar (P=0.874) (Table 3).

Many studies have been published regarding the preventive role of NSAIDs in patients undergoing ERCP. Murray et al. compared the use of 100 mg of rectally administered diclofenac versus placebo in the recovery area after ERCP.[17]

In 2007, Sotoudehmanesh et al. compared the use of 100 mg of rectal indomethacin with placebo, administered immediately before the ERCP. They enrolled a heterogeneous group of 442 patients. The incidence of PEP in the placebo group was 6.8 % (15/221) and 3.2 % (7/221) in the indomethacin group (P = 0.06).The incidence of pancreatitis in the no drug group (group C) was 16.4 % (20/122) and 7.8% (19/225) in indomethacin group in our study (P=0.014).

In 2007, Cheon et al. published the results of a clinical trial in the USA; found the incidence of pancreatitis in high-risk patients in the placebo group was 18% (16/89) and 17.8% (16/90) in the diclofenac group. The difference in the incidence and severity of pancreatitis between the two treatment groups was not significant.[20] Otsuka et al. compared the administration of 50 mg transrectal diclofenac against placebo (glycerin suppository) in 104 patients, applied 30 minutes before ERCP. They found an incidence of pancreatitis of 3.9% (2/51) for the diclofenac group and 18.9 % (10/53) in the control group (P = 0.017).[21]This study also well coincided with our study.

Elmunzer et al. conducted the most important controlled clinical trial, in 602 patients and compared 100 mg transrectal indomethacin against placebo (glycerin suppository).[18]Abu-Safieh et al. conducted a randomized doubleblind controlled trial in Palestine, including a total of 182 patients and comparing the intramuscular administration of 75 mg diclofenac with 3 ml of isotonic saline as a placebo. They reported an overall incidence of PEP of 10 %, 6.9 (6/89) for the diclofenac group and 12.9 % (12/93) for the placebo group. There was no significance difference in the incidence of PEP between the two groups (P = 0.164).[22]

From 2008 to the present, at least 10 meta-analyses have evaluated the results of the different clinical trials that have been reported. The results allow us to conclude that NSAIDs such as indomethacin or diclofenac used in the different routes of administration reduce the incidence of asymptomatic hyperamylasemia, pancreatitis and moderate to severe episodes of pancreatitis.[23-30]The results of our study are relevant because the drug was administrated immediately after completion of the endoscopic procedure, as was performed by Khoshbaten [31]and Elmunzer [19].

Traditionally, it has been considered that the placement of a small caliber (5 Fr) stent in the pancreatic duct was the standard treatment to prevent this complication. It has also been recommended in the management guidelines for the prevention of pancreatitis in patients considered to be at high risk.[5,6,32]In our study, pancreatic stenting was only used to treat pancreatic fistulas.Recently, Akbar and colleagues published the results of a meta-analysis in which a total of 29 studies were included (22 with pancreatic stent placement and 7 with the use of NSAIDs), showing that stenting or transrectal administration of NSAIDs was superior to placebo in the prevention of PEP. The combination of transrectal application of NSAIDs and the use of stents showed no greater effectiveness in the prevention of PEP when compared with that of each intervention alone. The results further demonstrated that transrectally administered NSAIDs alone were superior to pancreatic stenting in preventing PEP (OR 0.48, 95 % CI, 0.26 to

0.87) and must be regarded as the first-line preventive therapy.[25] This meta-analysis also supports our study result.

However, to support the previous conclusion, a high quality multicenter randomized clinical trial is required to better understand the efficacy of pancreatic stents with and without rectal NSAIDs and with rectal NSAIDs alone to prevent PEP in high-risk patients.

Conclusions:

This study showed that diclofen/indomethacin administered rectally immediately after ERCP reduced the incidence of PEP in high-risk patients.

Conflict of Interest:

The author stated that there is no conflict of interest in this study

Funding:

No specific funding was received for this study.

Ethical consideration:

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

References:

1. Freeman ML. Complications of endoscopic retrograde cholangiopancreatography: avoidance and management. Gastrointes Endosc Clin N Am. 2012;22: 567-86. https://0-doi-org.libus.csd.mu.edu/10.1016/j.giec.2012.05.001 PMid:22748249
2. Balmadrid B, Kozarek R. Prevention and management of adverse events of endoscopic retrograde cholangiopancreatography. Gastrointest Esdosc Clin N Am. 2013;23:385-403. https://0-doi-org.libus.csd.mu.edu/10.1016/j.giec.2012.12.007 PMid:23540966
3. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med. 1996;335:909-18. https://0-doi-org.libus.csd.mu.edu/10.1056/NEJM199609263351301 PMid:8782497
4. Masci E, Mariani A, Curioni S, Testoni PA. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. Endoscopy. 2003;35:830-4. https://0-doi-org.libus.csd.mu.edu/10.1055/s-2003-42614. PMid: 14551860
5. Dumonceau JM, Andriulli A, Deavere J, Mariani A, Rigaux J, Baron TH, et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. Endoscopy. 2010;42:503-15. https://0-doi-org.libus.csd.mu.edu/10.1055/s-0029-1244208 PMid:20506068
6. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: Management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400-16. https://0-doi-org.libus.csd.mu.edu/10.1038/ajg.2013.218 PMid:23896955
7. Cheon YK. Can post endoscopic retrograde cholangiopancreatography pancreatitis be prevented by a pharmacological approach? Korean J Intern Med. 2013;28:141-8. https://0-doi-org.libus.csd.mu.edu/10.3904/kjim.2013.28.2.141 PMid:23525264 PMCid:PMC3604601
8. Dumonceau JM, Rigaux J, Kahaleh M, Gomez CM, Vandermeeren A, Devière J. Prophylaxis of post-ERCP pancreatitis: a practice survey. Gastrointest Endosc. 2010;71:934-9. https://0-doi-org.libus.csd.mu.edu/10.1016/j.gie.2009.10.055 PMid:20226455
9. Hanna MS, Portal AJ, Dhanda AD, Przemioslo R. UK-wide survey on the prevention of post ERCP pancreatitis. Frontline Gastroenterol. 2014;5:103110. https://0-doi-org.libus.csd.mu.edu/10.1136/flgastro-2013-100323 PMid:24724007 PMCid:PMC3977499
10. Elmunzer BJ, Waljee AK, Elta GH, Taylor JR, Fehmi SM, Higgins PD. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. Gut. 2008;57:1262-7. https://0-doi-org.libus.csd.mu.edu/10.1136/gut.2007.140756 PMid:18375470
11. Dai HF, Wang XW, Zhao K. Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: A meta-analysis. Hepatobiliary Pancreat Dis Int. 2009;8:11-6.
12. Cotton PB, Lehman G, Vennes J,Geenen JE, Russell RC, Meyers WC et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991;37:383-93. https://0-doi-org.libus.csd.mu.edu/10.1016/S0016-5107(91)70740-2
13. Rustagi T, Jamidar PA. Endoscopic Retrograde Cholangiopancreatography-Related Adverse Events: General Overview. Gastrointest Endosc Clin N Am. 2015;97:97-110. https://0-doi-org.libus.csd.mu.edu/10.1016/j.giec.2014.09.005. PMid:25442961
14. Rustagi T, Jamidar PA. Endoscopic Retrograde Cholangiopancreatography (ERCP)-Related Adverse Events: Post-ERCP Pancreatitis. Gastrointest Endosc Clin N Am. 2015;97:107-21. https://0-doi-org.libus.csd.mu.edu/10.1016/j.giec.2014.09.006. PMid: 25442962
15. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc. 1991;37:383-93. https://0-doi-org.libus.csd.mu.edu/10.1016/S0016-5107(91)70740-2
16. Cooper ST, Slivka A. Incidence, risk factors, and prevention of post-ERCP pancreatitis. Gastroenterol Clin North Am. 2007;36:259-76. https://0-doi-

org.libus.csd.mu.edu/10.1016/j.gtc.2007.03.006. PMid:17533078.

17. Murray B, Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology. 2003;124:1786-91. https://0-doi-org.libus.csd.mu.edu/10.1016/S0016-5085(03)00384-6

18. Sotoudenhmanesh R, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol. 2007;102:978-83. https://0-doi-org.libus.csd.mu.edu/10.1111/j.1572-0241.2007.01165.x PMid:17355281

19. Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. U.S. Cooperative for Outcomes Research in Endoscopy (SCORE). A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366:1414-22. https://0-doi-org.libus.csd.mu.edu/10.1056/NEJMoa1111103. PMid:22494121 PMCid: PMC 3339271

20. Cheon YK, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, et al. Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. Gastrointest Endosc. 2007;66:1126-32. https://0-doi-org.libus.csd.mu.edu/10.1016/j.gie.2007.04.012 PMid:18061712

21. Otsuka T, Kawazoe S, Nakashima S, Kamachi S, Oeda S, Sumida C, et al. Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a randomized controlled trial. J Gastroenterol. 2012;47:912-7. https://0-doi-org.libus.csd.mu.edu/10.1007/s00535-012-0554-7 PMid:22350703

22. Abu-Safieh Y, Altiti R, Lobadeh M. Diclofenac vs. Placebo in a randomized double-blind controlled trial, in post ERCP pancreatitis. Am J Clin Med Res. 2014;2:43-6. https://0-doi-org.libus.csd.mu.edu/10.12691/ajcmr-2-2-1

23. Zheng MH, Xia HH, Chen YP. Rectal administration of NSAIDs in the prevention of post-ERCP pancreatitis: a complementary meta-analysis. Gut. 2008;57:1632-3.

24. Ding X, Chen M, Huang S, Zhang S, Zou X. Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: a meta-analysis. Gastrointest Endosc. 2012;76:1152-9. https://0-doi-org.libus.csd.mu.edu/10.1016/j.gie.2012.08.021. PMid:23164513

25. Akbar A, Abu Dayyeh BK, Baron TH, Wang Z, Altayar O, Murad MH. Rectal nonsteroidal anti-inflammatory drugs are superior to pancreatic duct stents in preventing pancreatitis after endoscopic retrograde cholangiopancreatography: a network meta-analysis. Clin Gastroenterol Hepatol. 2013;11:778-83. https://0-doi-org.libus.csd.mu.edu/10.1016/j.cgh.2012.12.043. PMid:23376320

26. Yaghoobi M, Rolland S, Waschke KA, McNabb-Baltar J, Martel M, Bijarchi R, et al. Meta-analysis: rectal indomethacin for the prevention of post-ERCP pancreatitis. Aliment Pharmacol Ther. 2013;38:995-1001. https://0-doi-org.libus.csd.mu.edu/10.1111/apt.12488. PMid:24099466

27. Sun HL, Han B, Zhai HP, Cheng XH, Ma K. Rectal NSAIDs for the prevention of post-ERCP pancreatitis: A meta-analysis of randomized controlled trials. Surgeon. 2014;12:141-7. https://0-doi-org.libus.csd.mu. edu/10.1016/j.surge.2013.10.010. PMid: 24332479

28. Sethi S, Sethi N, Wadhwa V, Garud S, Brown A. A meta-analysis on the role of rectal diclofenac and indomethacin in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Pancreas. 2014;43:190-7. https://0-doi-org.libus.csd.mu.edu/10.1097/MPA.0000000000000090. PMid:24518496

29. Ahmad D, Lopez KT, Esmadi MA, Oroszi G, Matteson-Kome ML, Choudhary A, et al. The Effect of indomethacin in the prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis. Pancreas. 2014;43:338-42. https://0-doi-org.libus.csd.mu.edu/10.1097/MPA. 0000000 000000086. PMid:24622061

30. Puig I, Calvet X, Baylina M, Isava A, Sort P, Llaó J, et al. How and When Should NSAIDs Be Used for Preventing Post-ERCP Pancreatitis? A Systematic Review and Meta-Analysis. PLoS One. 2014;9, e92922. https://0-doi-org.libus.csd.mu.edu/10.1371/journal.pone.0092922. PMid:24675922 PMCid: PMC 3968039

31. Khoshbaten M, Khorram H, Madad L, Ehsani Ardakani MJ, Farzin H, Zali MR. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol. 2008;23:e11-6. https://0-doi-org.libus.csd.mu.edu/10.1111/j.1440-1746.2007.05096.x. PMid:17683501

32. Mazaki T, Mado K, Masuda H, Shiono M. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: An updated meta-analysis. J Gastroenterol. 2013;49:343-55. https://0-doi-org.libus.csd.mu.edu/10.1007/s00535-013-0806-1. PMid:23612857