Title

Efficacy of low dose rectal diclofenac for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: A propensity score-matched analysis

Running title

Efficacy of low dose NSAIDs for preventing PEP

Authors name

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Disclosures

The authors have no conflicts of interest or financial ties to disclosure.

Each authors specific contributions to the works

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Abstract

Background: Acute pancreatitis is a major adverse event of endoscopic retrograde cholangiopancreatography (ERCP). Rectal administration of non-steroidal anti-inflammatory drugs (NSAIDs) decreases the incidence of post-ERCP pancreatitis (PEP). However, the efficacy of low dose rectal NSAIDs for preventing PEP remains controversial.

Methods: We performed a retrospective study of 301 patients with native papilla and a body weight of less than 50 kg who underwent ERCP between September 2010 and October 2019. After July 2016, a 25 mg dose of rectal diclofenac was routinely administered within 15 minutes before ERCP (NSAIDs group, n = 72) and the control group (n=229) consisted in patients undergoing ERCP before this date without treatment. We compared the incidence of PEP between the two groups using propensity score-matching.

Results: A total of 66 pairs of patients in each group were selected. The patients and procedural-related factors were similar in both groups. In total, 15 patients (11.4%) developed PEP: 12.1% (8/66) in the NSAIDs group and 10.6% (7/66) in the control group (Odds ratio (OR) 1.2; 95% confidence interval (CI) 0.4-3.5; p=0.78).

There was no significant difference in incidence of other adverse events related to ERCP between the two groups.

Conclusions: Prophylactic administration of a 25mg dose of rectal diclofenac did not reduce the incidence of PEP in patients with a native papilla and a body weight of less than 50 kg in this study and a certain dose of rectal NSAIDs, such as a 100-mg dose, should be administered regardless of body weight to prevent PEP.

Key words: Low dose, diclofenac, post-ERCP pancreatitis

Introduction

Acute pancreatitis is the most important adverse event (AE) of endoscopic retrograde cholangiopancreatography (ERCP), and post-ERCP pancreatitis (PEP) occurs in 1–25% of patients [1-2]. Although PEP is usually mild or moderate, severe pancreatitis may develop in some cases, which requires further intervention and leads to death in 0.3–0.6% of the patients [3-6].

Numerous pharmacological agents have been evaluated for the prevention of PEP. Several randomized trials have confirmed the efficacy of rectal non-steroidal anti-inflammatory drugs (NSAIDs) in preventing PEP [7-10]. Routine rectal administration of diclofenac or indomethacin, immediately before an ERCP has been recommended to minimize the risk of PEP in the European Society of Gastrointestinal Endoscopy (ESGE) and Japanese Society of Hepato-Biliary-Pancreatic Surgery (JHBPS) guidelines [11] [12].

However, the recommended dose, and that used in these trials, of rectal NSAIDs is 100 mg, which is higher than the 25 mg dose that is usually administered in cases with a body weight less than 50 kg in Japan. But the efficacy of low dose rectal NSAIDs is unclear. The aim of the present study was to evaluate the efficacy of a 25 mg dose of rectal diclofenac for the prevention of PEP compared to a control

group of patients without prophylactic rectal diclofenac suppository.

Methods

Patients

Consecutive patients who underwent ERCP with a native papilla and body weight of less than 50 kg between September 2010 and October 2019 at Okayama University Hospital were included in this study. Among them, patients who met the following criteria were excluded: (1) presence of acute pancreatitis; (2) presence of chronic pancreatitis or pancreatic head tumor with occlusion of the main pancreatic duct (at low risk of PEP); and (3) contraindication to NSAIDs (in the NSAIDs group).

In our institute, we prospectively administered a 25 mg dose of diclofenac suppository in patients whose body weight was less than 50 kg and a 50 mg dose of diclofenac suppository in patients whose body weight was greater than 50 kg within 15 minutes before ERCP to prevent PEP after July 2016. We did not administer prophylactic diclofenac suppository prior to this date. Thus, we divided the eligible patients into two groups based on the administration of diclofenac (NSAIDs group and control group) and accordingly compared the incidence of PEP. This study was approved by the ethics committee of our hospital.

Intervention

ERCP was performed with the patients in a prone or semi-prone position, under conscious sedation, and with CO_2 insufflation. Pharyngeal anesthesia was induced by a topical anesthetic using a lidocaine spray, whereas conscious sedation was induced by an intravenous medication, mainly pethidine hydrochloride, and diazepam, just before the procedures. All ERCP procedures were carried out with a standard duodenoscope (TJF-260V or JF-260V; Olympus Medical System, Tokyo, Japan).

The ERCP devices used were not limited to any specific types. We used a conventional cannulation technique that involved contrast injection at the first attempt, without the use of a guidewire. Injection of the contrast medium allowed visualization of the bile duct or pancreatic duct in order to confirm whether selective cannulation was achieved. In cases that were difficult to cannulate, we used pancreatic guidewire placement or pre-cut sphincterotomy to achieve selective cannulation. Pancreatic duct stenting was performed to prevent pancreatitis at the endoscopist's discretion. We administered 20 mL of ulinastatin (150,000 U) solution, a protease inhibitor, by intravenous infusion immediately after the ERCP,

which is routinely used in our institution with the expectation that it will prevent PEP. All patients received intravenous 80 mL/h of Ringer's lactate solution during the procedures generally and none of the patients received pre-procedural or post-procedural aggressive hydration. After the procedures, the endoscopist recorded the results, and the patients fasted until the blood tests that were performed the following day confirmed the absence of pancreatitis or other AEs and resumed eating on the following day. For the purpose of observation, all of the patients in this study were hospitalized for at least 48 hours after the procedure. We assessed the patients the morning after the procedure and whenever the patients complained of pain. Abdominal pain was defined as new or worsening persistent pain in the epigastric region lasting more than 24 hours. Decisions regarding the evaluation of AEs following the procedure were left to the discretion of the endoscopist.

Endpoints

Primary and secondary endpoints

The primary endpoint was the occurrence of PEP. PEP was defined by the criteria set by Cotton et al. (13), as the development of abdominal pain and elevation of serum

amylase levels by more than 3 times the upper normal limit (hyperamylasemia) within 24 hours after an ERCP. The serum amylase level was measured before the ERCP, and when the patients complained of abdominal pain within 24 hours after the ERCP; otherwise, it was routinely measured 24 hours after the ERCP. The secondary endpoints included the development of moderate or severe PEP. The severity of PEP was graded according to the American Society for Gastrointestinal Endoscopy lexicon for endoscopic adverse events (14).

The patient- and procedure-related factors were recorded at the end of procedures and compared between the two groups. Patient-related factors included the following: (1) age, (2) sex, (3) indication for ERCP, and (4) presence of previous pancreatitis. Procedure-related factors include the following: (1) main target duct, (2) pre-cut sphincterotomy, (3) endoscopic pancreatic sphincterotomy (EPS), (4) time for selective cannulation to the targeted duct initiated when cannulation was attempted, (5) presence of juxta papillary diverticulum, (6) endoscopic biliary sphincterotomy, (7) bile duct-intraductal ultrasonography, (8) endoscopic biliary drainage, (9) endoscopic papillary balloon dilation (EPBD) of the intact biliary sphincter , (10) injection of contrast agent into the pancreatic duct, (11) pancreatic

guidewire passage, (12) pancreatic duct stenting, and (13) total time for the ERCP procedure. The following factors were considered to be high risk for the occurrence of PEP: (1) clinical suspicion of sphincter of Oddi dysfunction (SOD), (2) female sex,(3) previous pancreatitis, (4) difficult cannulation (where successful selective cannulation took more than 10 minutes) or failed cannulation, (5) injection of contrast agent into the pancreatic duct, and (6) pancreatic guidewire passage (15).

Statistical analysis

Non-continuous variables were compared using the χ^2 test, while continuous variables were compared using the Wilcoxon rank-sum test. A p-value < 0.05 was considered as statistically significant.

We performed a propensity score matching analysis to control and reduce the confounding bias in each group and we compared the specific frequencies of PEP between the two groups with a similar background. A total of eight variables, namely, six definite risk factors for PEP (clinical suspicion of SOD, sex, history of pancreatitis, difficult cannulation, injection of the contrast agent into the pancreatic duct, and pancreatic guidewire passage) and two factors (main target duct and presence of endoscopic pancreatic stenting), which were imbalanced in baseline clinical characteristics and could possibly influence the frequency of PEP, were used to generate a propensity score using a multivariate logistic regression model. The

propensity score model was well calibrated and discriminated well between the NSAID and control groups (*c*-statistics = 0.69). The c-statistic was calculated by measuring the receiver-operating characteristic curve to assess the validity of the model. The patients were matched one-to-one using the nearest neighbor algorithm without replacement and a caliper width of 0.2 of the pooled standard deviation of the logit of the calculated propensity score. Absolute standardized differences (ASD) were estimated before and after matching to evaluate the balance of the histological findings of the enrolled patients in the NSAID and control groups. An ASD greater than 0.25 was considered to indicate a large imbalance. In the ancillary analysis, differences in PEP frequencies between the NSAID and control groups were tested in all cases by univariate logistic regression analysis. Moreover, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using the multivariate logistic regression model adjusting for eight variables that were used to generate a propensity score. All statistical analyses were performed using the JMP 12 software (SAS Institute Inc., Cary, NC, USA). Ranges of continuous variables are shown as interquartile ranges.

Results

Patients

Between July 2010 and October 2019, 423 patients with native papilla and with a body weight less than 50 kg were scheduled to undergo ERCP and assessed for eligibility. Among them, 122 patients (28.8%) were excluded for fulfilling one of

previously outlined exclusion criteria (7 had presence of acute pancreatitis, 7 had presence of chronic pancreatitis, 95 had presence of pancreatic head tumor with occlusion of the main pancreatic duct, and 13 presented with contraindication for NSAIDs: renal failure (n=4), poor general condition due to severe comorbidity (n=4), NSAIDs allergy (n=3) and aspirin-induced asthma (n=2). Finally, the total number of patients included in the analysis was 301 (72 in the NSAID group vs. 229 in the control group) (Figure 1).

Demographic characteristics and endoscopic procedures

The baseline characteristics of all patients (n = 301) are shown in Table 1. The NSAID group had higher proportions of female patients, patients with endoscopic biliary drainage, and patients with pancreatic duct stent placement, and lower prevalence of juxta papilla diverticulum than the control group. Moreover, examination in the NSAID group targeted the common bile duct more frequently and had a longer total procedure time. Among them, the higher frequency of pancreatic duct stenting in the NSAID group than in the control group was due to differences in the historical background. The 2 groups were similar with respect to the other variables.

After one-to-one propensity score-matching using eight factors, 66 pairs were selected from each group. The baseline characteristics of the 2 groups were comparable (Table 2). The number of patients at high risk of PEP was 62 (93.9%) and 62 (93.9%) in the NSAID and control groups, respectively (p = 1.00).

Study outcomes

The primary endpoint of PEP after the propensity score matching occurred in 15 (11.4%) of the 132 patients, including 8 (12.1%) of the 66 patients in the NSAID group and 7 (10.6%) of the 66 patients in the control group (OR 1.2, 95%CI 0.4-3.4, p = 0.78). Severe or moderate PEP occurred in 4 patients (6.1%) in the NSAID group and 3 patients (4.6%) in the control group (OR 1.4, 95%CI 0.3-7.1, p = 0.70). All patients with PEP were discharged within 30 days after ERCP. There were no statistical differences in incidence and severity of PEP between the two groups. Low dose rectal NSAIDs did not significantly reduce the incidence of PEP and did not significantly improve the severity of PEP (Table 2).

Result of the ancillary analysis

PEP occurred in 12.3% (37/301) of the patients. Of these, 9 (12.5%) of the 72 patients

developed PEP in the NSAID group and 28 (12.2%) of the 229 patients in the control group ((OR 1.02; 95% CI 0.44-2.21; p = 0.95)). Similarly, low-dose rectal NSAIDs did not significantly reduce the incidence of PEP in multivariate analysis when adjusted for eight variables (OR 0.92; 95% CI 0.39-2.34; p = 0.92), which was the same as the result after propensity score matching.

Other adverse events

The median serum amylase level after the procedures was 132 (77–543) IU/L in the NSAIDs group and 133 (76–256) IU/L in the control group (p = 0.44), and hyperamylasemia was observed in 20 patients (30.3%) in the NSAIDs group and 11 patients (16.7%) in the control group (p = 0.06). Moreover, there was no significant difference between the two groups in terms of bleeding, perforation, and biliary infection (Table 2).

Discussion

In some randomized controlled trials, rectal NSAIDs have shown significantly better prophylactic activity in PEP than that shown by placebo (7-10) and have been recommended to be administered in all patients without contraindications to

NSAIDs in the ESGE and JHBPS guidelines (11, 12). In this retrospective study, the rectal administration of very low dose (25 mg) NSAIDs did not prevent the occurrence of PEP.

In nearly all previous studies performed in Western countries, the dose of rectal NSAIDs was 100 mg, which is different to that used in the present study (25 mg) (7-10). In Japan, it is recommended to administer a rectal dose of NSAIDs of 0.5–1.0 mg per kg body weight; a dose of 100 mg is considered too high in Japan, where the majority of the people are under 100 kg, and a 25 mg dose is usually administered to patients who are less than 50 kg because the side effects of NSAIDs are dose dependent (16). Only a few studies have evaluated the effects of rectal NSAIDs for preventing of PEP at doses other than 100 mg, and the optimal dose of rectal NSAIDs is uncertain.

Recently, a large scale multicenter randomized trial was conducted to compare the efficacy of high-dose regimen (200 mg) and standard-dose regimen (100 mg) of rectal NSAIDs on the frequency of PEP, and the high-dose regimen did not appear to offer any advantage over the standard-dose regimen (17). This result suggests

that the effect of NSAIDs in preventing PEP may not be dose dependent, and if low dose rectal NSAIDs can prevent PEP as well as the standard dose, it is likely to be safer than a standard dose.

Two RCTs have evaluated the effect of low dose rectal NSAIDs (25 mg or 50 mg) on preventing PEP (18,19). Otsuka et al. reported that the occurrence of PEP among patients who received rectal diclofenac tended to be lower than in those who did not (2/51 [3.9%] vs. 10/53 [18.9%]; p=0.017). Conversely, Katoh et al. reported no difference among the two groups (8/147 [5.4%] in the diclofenac group and 5/150 [3.3%] in the control group, p = 0.286). The former report had a small number of participants and the trial was performed at a center with a low volume of ERCP cases, while in the latter report, approximately half of the registered cases were low-risk patients, including those with non-native papilla and pancreatic head cancer; thus, the effect of low dose rectal NSAID administration remains controversial. In this study, the majority of the enrolled patients had a risk factor for PEP, as opposed to the previous two RCTs, and there was no significant difference in the patient characteristics for adjustment by propensity score-matching.

Our study has some limitations. First, this study was retrospective in nature and was performed in a single center. Second, no conclusions could be drawn on the preventive effect of low-dose rectal NSAIDs on PEP owing to the small sample size. Therefore, a prospective, randomized, non-inferiority or equivalence trial involving a sufficient number of patients is required to confirm our results and further study evaluating the optimal dose of rectal NSAIDs for preventing PEP is needed.

In conclusion, prophylactic administration of a 25mg dose of rectal diclofenac did not reduce the incidence of PEP in patients with a native papilla and a body weight of less than 50 kg in this study. We considered that very low doses of NSAIDs (25 mg) cannot prevent PEP based on the results of this study, and a certain dose of rectal NSAIDs, such as a 100 mg dose, should be administered immediately before ERCP in patients without contraindications to NSAIDs regardless of body weight to prevent PEP.

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Table 1. Patient and procedure-related factors of NSAIDs and control groups

	All patients				Propensity-matched patients			
	NSAIDs group (n=72)	Control group (n=229)	P-value	ASD	NSAIDs group (n=66)	Control group (n=66)	P-value	ASD
Patient-related factors								
Body weight, Kg (range)	45(42-48)	45(41-47)	0.43	0.125	44 (42-48)	44 (41-47)	0.38	0.155
Age, year, median (range)	72(59-79)	71(62-78)	0.48	0.069	74 (62-80)	70 (62-77)	0.32	0.106
Sex, Female, n (%)	62(86.1%)	166(72.5%)	0.02	0.340	56 (84.9%)	56 (84.9%)	1.00	0.000
Indication, n (%)			0.40	0.106			-	N.A*
Suspected for SOD	2 (2.8%)	3(1.3%)			0 (0%)	0 (0%)		
Other disease	70 (97.2%)	226 (98.7%)			55 (100%)	55 (100%)		
Malignant biliary disease	27 (37.5%)	66(28.8%)			25 (37.9%)	25 (37.9%)		
Common bile duct stone	17 (23.6%)	42(18.3%)			15 (22.7%)	12 (18.2%)		
Other benign biliary disease	12 (16.7%)	44(19.2%)			12 (18.2%)	15 (22.7%)		
PDAC	5 (6.9%)	32(14.0%)			5 (7.6%)	4 (6.1%)		
IPMN	7 (9.7%)	17(7.4%)			7 (10.6%)	1 (1.5%)		
Other pancreatic disease	2 (2.8%)	25(10.9%)			2 (3.0%)	8 (12.1%)		
History of recurrent pancreatitis, n (%)	1 (1.4%)	7 (3.1%)	0.44	0.113	1 (1.5%)	1 (1.5%)	1.00	0.000
Procedures-related factors								
Main target duct, n (%)			0.01	0.397			1.00	0.000
Common bile duct	61 (84.7%)	156(68.1%)			55 (83.3%)	55 (83.3%)		
Pancreatic duct	11 (15.3%)	73(31.9%)			11 (16.7%)	11 (16.7%)		
Success rate of selective cannulation, n (%)	71 (98.6%)	221(96.5%)	0.36	0.136	65 (98.5%)	63 (95.5%)	0.31	0.177
Precut sphincterotomy, n (%)	9 (12.5%)	24(10.5%)	0.63	0.063	9 (13.6%)	9 (13.6%)	1.00	0.000
Endoscopic pancreatic sphincterotomy, n (%)	3 (4.2%)	12(5.2%)	0.72	0.051	2 (3.0%)	5 (7.6%)	0.24	0.204
Time for selective cannulation, min (range)	7 (3-19)	5(2-14)	0.11	0.234	7 (3-19)	7 (3-17)	0.86	0.208
Difficult cannulation, n (%)	31 (43.1%)	84(36.7%)	0.33	0.130	27 (40.9%)	29 (43.9%)	0.72	0.051
Presence of juxta papilla diverticulum, n (%)	17 (23.6%)	29(12.7%)	0.02	0.286	13 (19.7%)	14 (21.2%)	0.83	0.037
Endoscopic biliary sphincterotomy, n (%)	39 (54.2%)	101(44.1%)	0.14	0.201	35 (53.0%)	28 (42.4%)	0.22	0.213
Common bile duct-intraductal ultrasonography, n (%)	18 (25.0%)	72 (31.4%)	0.30	0.143	15 (22.7%)	21 (31.8%)	0.24	0.205
Endoscopic biliary drainage, n (%)	36 (50.0%)	83(36.2%)	0.04	0.279	32 (48.5%)	26 (39.45)	0.29	0.183
EPBD of intact biliary sphincter, n (%)	1 (1.4%)	3(1.3%)	0.96	0.007	1 (1.5%)	1 (1.5%)	1.00	0.000
Pancreatic injection, n (%)	45 (62.5%)	148(64.6%)	0.74	0.044	39 (59.1%)	39 (59.1%)	1.00	0.000

Pancreatic guidewire passage, n (%)	34 (47.2%)	92(40.2%)	0.29	0.142	28 (42.4%)	28 (42.4%)	1.00	0.000
Placement of pancreatic duct stent, n (%)	22 (30.6%)	30(13.1%)	0.0006	0.430	16 (24.2%)	16 (24.2%)	1.00	0.000
ERCP procedure time, min (range)	36 (21–59)	29(18–47)	0.04	0.331	36 (22–57)	34 (23–46)	0.46	0.208
High risk state for PEP, n (%)	68 (94.4%)	214 (93.5%)	0.76	0.042	62 (93.9%)	62 (93.9%)	1.00	0.000
Patients with 1 risk factor for PEP	18 (25.0%)	60 (26.2%)			18 (29.0%)	18 (29.0%)		
Patients with 2 or more risks factors for PEP	50 (69.4%)	154 (67.3%)			44 (66.7%)	44 (66.7%)		

ASD; Absolute standardized difference, NSAIDs: Non-steroidal anti-inflammatory drugs, SOD: Sphincter of Oddi dysfunction, PDAC: Pancreatic ductal adenocarcinoma, IPMN: Intraductal papillary mucinous neoplasm, EPBD: Endoscopic papillary balloon dilation, ERCP: Endoscopic retrograde cholangiopancreatography, PEP: Post-ERCP pancreatitis, N.A: not available

* Since the denominator is zero, the ASD cannot be calculated.

Table 2. Incidence of post-ERCP pancreatitis and other adverse events

	NSAIDs group n=66	Control group n=66	P-value	OR	95%CI
Post-ERCP pancreatitis in all patients, n (%)	8 (12.1%)	7 (10.6%)	0.78	1.2	0.4-3.5
Mild	4 (6.1%)	4 (6.1%)	1.00	1.0	0.2-4.4
Moderate or severe	4 (6.1%)	3 (4.6%)	0.70	1.4	0.3-7.1
Other adverse events, n (%)					
Hyperamylasemia	20 (30.3%)	11 (16.7%)	0.06	2.2	0.9-5.1
Bleeding	1 (1.5%)	1 (1.5%)	1.00	1.0	0.04-25.6
Perforation	0 (0%)	0 (0%)	N.A		
Biliary infection	1 (1.5%)	0 (0%)	0.23	N.A	N.A

ERCP: Endoscopic retrograde cholangiopancreatography, NSAIDs: Non-steroidal anti-inflammatory drugs, OR: odds ratio, CI: confidence interval, NA: not available

Figure legend

Figure 1: Flow chart of the patient selection process.

ERCP: Endoscopic retrograde cholangiopancreatography, NSAIDs: Non-steroidal anti-inflammatory drugs