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【 ORIGINAL ARTICLE 】

The Effectiveness of the Rectal Administration of Low-dose Diclofenac for the Prevention of Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis

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Abstract:

Objective A 50-100-mg rectal dose of nonsteroidal anti-inflammatory drugs (NSAIDs; diclofenac or indomethacin) has been shown to prevent post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). However, this is higher than the recommended 25-mg dose that is commonly administered to Japanese patients. The objective of this study was to evaluate the safety and efficacy of 25-mg rectal dose of diclofenac in preventing PEP.

Methods Between January 2016 and March 2017, a total of 147 patients underwent ERCP with or without the rectal administration of diclofenac (25 mg) 20 min before the procedure. A retrospective analysis was conducted to evaluate the efficacy and safety of this dose in preventing PEP.

Results Thirteen patients (8.8%) developed PEP: 3 patients (4.1%) in the diclofenac group and 10 (13.7%) in the control group (p=0.0460). After ERCP, there were no cases of gastrointestinal hemorrhage, ulceration, acute renal failure, or death. A multivariate logistic regression analysis revealed that the non-administration of rectal diclofenac was a risk factor for PEP (odds ratio=3.530; 95% confidence interval=1.017-16.35; p=0.0468).

Conclusions A 25-mg rectal dose of diclofenac might prevent PEP.

Key words: diclofenac, ERCP, post-ERCP pancreatitis, prevention, 25-mg dose

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Introduction

Acute pancreatitis is a major and important adverse side effect of endoscopic retrograde cholangiopancreatography (ERCP). Post-ERCP pancreatitis (PEP) occurs in 1-9% of patients and can progress to a severe condition or cause death (1, 2). Numerous clinical and pharmacologic studies have been performed with the aim of preventing PEP (1-5). In recent years, some randomized controlled trials and meta-analyses reported that a 50-100-mg rectal dose of nonsteroidal anti-inflammatory drugs (NSAIDs) can prevent PEP (6-8). A 100-mg rectal dose of NSAIDs (diclofenac or indomethacin) is recommended in Western countries; however, this is higher than the recommended 25-mg dose that is used in Japan, especially in elderly patients because of their age and lower body weight. A previous study reported that administration of a 50-mg rectal dose of diclofenac was safe and effective in Japanese patients (9); however, the efficacy of a lower, 25-mg, dose is still unclear. The objective of this study was to evaluate the efficacy and safety of a 25-mg rectal dose of diclofenac in the prevention of PEP.

Materials and Methods

Patients

A retrospective analysis of all ERCP procedures performed at Takayama Red Cross Hospital from January 2016 to March 2017 was conducted to identify patients. In August

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2016, after the 2015 Japanese guidelines for the management of acute pancreatitis (10) were published, the administration of diclofenac was approved by the Institutional Review Board (IRB). Hence, after August 2016, we started to administer a 25-mg dose of diclofenac to patients undergoing ERCP. Patients were eligible if they fulfilled the following criteria: 1) age ≥20 years, 2) normal upper intestinal anatomy, including patients who underwent Billroth I or II reconstruction. The exclusion criteria were as follows: 1) acute pancreatitis, 2) peptic ulcer disease, 3) NSAID allergy, 4) aspirin-induced asthma, and 5) severe kidney dysfunction. One hundred forty-seven patients were finally identified who underwent ERCP with or without the administration of a 25-mg rectal dose of diclofenac before ERCP. Informed consent for the endoscopic procedures and the rectal administration of diclofenac was obtained from all patients. This study was approved by the IRB and registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN 000026434).

Procedure

In our institution, around 140 patients undergo ERCP annually and all the ERCP procedures are performed by 4 operators who have experienced more than 500 ERCP procedures. All ERCP procedures were carried out with a standard duodenoscope (TJF-260V; Olympus Medical System, Tokyo, Japan) for patients with normal upper intestinal anatomy or Billroth I reconstruction, or with a gastroscope (GIF-2T240; Olympus Medical System) for patients with Billroth II reconstruction. The diclofenac group received a 25-mg rectal dose of diclofenac 20 minutes before ERCP. During ERCP, patients received intravenous midazolam and pentazocine whilst under constant sedation. The doses of midazolam and pentazocine were calculated by the main operator based on the patient's medical condition and age. Most patients received 5-10 mg of midazolam, and 7.5-15 mg of pentazocine. Antibiotics [sulbactam/cefoperazone (1 g)] and protease inhibitors [nafamostat mesylate (10 mg)] were also administered on 4 occasions: before, and after the procedure, and twice on post-operative day 1 in both groups. Routine blood tests, including the measurement of the patient's serum amylase levels, were performed before the procedure and on post-operative day 1 to monitor for possible adverse events. In patients with elevated serum amylase associated with abdominal pain after ERCP, computerized tomography (CT) was performed.

The baseline patient characteristics and outcomes of ERCP, including sex, age, body mass index (BMI), body surface area (BSA), Billroth I or II reconstruction, bile duct stone, history of pancreatic, hepatobiliary, or gastrointestinal cancer, history of PEP, first conducted ERCP, difficult cannulation, pancreatography, endoscopic sphincterotomy (ES), endoscopic papillary balloon dilation (EPBD), endoscopic papillary large balloon dilation (EPLBD), and bile duct or pancreatic duct stenting were retrospectively extracted from medical records. The time taken to perform ERCP (min) was defined as the interval from the insertion of the duodenoscope or gastroscope to its removal.

The occurrence of procedure-related adverse events was measured. All adverse events were classified according to the established criteria (1). Using these criteria, PEP was diagnosed if abdominal pain developed and the serum amylase level was three times (or greater) the upper normal limit (>375 IU/mL) within 24 hours of the ERCP procedure (1). In addition, diclofenac toxicities, including gastrointestinal hemorrhage/ulceration and acute renal failure, were measured.

Statistical analysis

The baseline patient characteristics and outcomes were compared between the diclofenac and control groups. Continuous variables were presented as the median and interquartile range. Fisher's exact test was used for the statistical analysis of categorical variables and the Wilcoxon rank sum test was used for continuous variables. The risk factors for PEP were initially evaluated by a univariate analysis. The predictive risk factors for PEP that had a p value of <0.05 in the univariate analysis were then included in a multivariate logistic regression analysis to determine the independent risk factors for PEP. In this analysis, odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. All statistical analyses were conducted using the JMP software program (version 8.0, SAS Institute, Cary, USA). p values of < 0.05 were considered to indicate statistical significance.

Results

During the study period, a total of 162 patients underwent ERCP. Among these patients, 147 fulfilled the inclusion criteria: 74 patients received a 25-mg rectal dose of diclofenac before ERCP (diclofenac group) and 73 patients underwent ERCP without receiving diclofenac (control group). The baseline characteristics of the patients are summarized in Table 1. There were no significant differences between the diclofenac and control groups with respect to sex, age, BMI, BSA, Billroth I or II reconstruction, biliary stone, history of hepatobiliary, pancreatic, or gastrointestinal cancers, history of PEP, first conducted ERCP, difficult cannulation, pancreatography, ES, EPBD, EPLBD, bile duct or pancreatic duct stenting, or ERCP procedure duration (min). The median BMI and BSA did not differ to a statistically significant extent between the two groups: 21.5 kg/m^2 (BMI), 1.43 m^2 (BSA) in the diclofenac group and 20.0 kg/m^2 (BMI), 1.43 m^2 (BSA) in the control group (p=0.332 and 0.632, respectively).

Adverse events

PEP occurred in 13 of the 147 patients (8.8%); the incidence in the diclofenac group [3 patients (4.1%)] was significantly lower than that in the control group [10 patients (13.7%)] (p=0.0460). In the diclofenac group, PEP was mild in 1 patient and severe in 2 patients. In contrast, PEP was

Table 1. The Baseline Patient Characteristics.

	Diclofenac group (n=74)	Control group (n=73)	p value
Female, n (%)	39 (52.7%)	37 (50.7%)	0.869
Age (years), median (IQR)	78 (48-95)	83 (46-99)	0.0860
BMI (kg/m^2), median (IQR)	21.5 (12.8-33.2)	20.0 (10.2-28.6)	0.332
BSA (m^2), median (IQR)	1.43 (1.09-1.99)	1.43 (1.00-2.34)	0.632
Billroth I reconstruction, n (%)	1 (1.4%)	2 (2.7%)	0.620
Billroth II reconstruction, n (%)	1 (1.4%)	2 (2.7%)	0.620
Biliary stone, n (%)	45 (60.8%)	48 (65.8%)	0.609
Cancer, n (%)	29 (39.2%)	25 (34.2%)	0.609
History of PEP, n (%)	6 (8.1%)	9 (12.3%)	0.428
First ERCP, n (%)	37 (50.0%)	37 (50.7%)	1.00
Difficult cannulation, n (%)	14 (18.9%)	12 (16.4%)	0.829
Pancreatography, n (%)	17 (23.0%)	16 (21.9%)	1.00
ES, n (%)	35 (47.3%)	31 (42.5%)	0.620
EPBD, n (%)	0 (0%)	4 (5.5%)	0.0580
EPLBD, n (%)	8 (10.8%)	7 (9.6%)	1.00
Biliary stent placement, n (%)	36 (48.7%)	32 (43.8%)	0.621
Pancreatic stent placement, n (%)	1 (1.4%)	0 (0%)	1.00
Procedure duration (min), median (IQR)	21 (4-117)	23 (7-90)	0.513

IQR: interquartile range, BMI: body mass index, BSA: body surface area, ERCP: endoscopic retrograde cholangiopancreatography, ES: endoscopic sphincterotomy, EPBD: endoscopic papillary balloon dilation, EPLBD: endoscopic papillary large balloon dilation

Table 2. Summary of Adverse Events.

	Diclofenac group (n=74)	Control group (n=73)	p value
PEP	3 (4.1%)	10 (13.7%)	0.0460*
Mild, n (%)	1 (1.4%)	7 (9.6%)	0.0335*
Moderate, n (%)	0 (0%)	3 (4.1%)	0.120
Severe, n (%)	2 (2.7%)	0 (0%)	1.00
Hemorrhage of major papilla, n (%)	2 (2.7%)	1 (1.4%)	1.00

*p<0.05. ERCP: endoscopic retrograde cholangiopancreatography, PEP: post-ERCP pancreatitis

mild in 7 patients and moderate in 3 patients in the control group. There was no significant difference in the occurrence of moderate or severe PEP between the diclofenac [2 patients (2.7%)] and control [3 patients (4.1%)] groups. Hemorrhage of the major papilla after ES occurred in 2 (2.7%) patients in the diclofenac group, and 1 (1.4%) patient in the control group; and was mild in both groups (Table 2). With regard to adverse events after ERCP, there were no cases of gastrointestinal hemorrhage, ulceration, acute renal failure, or death in either group.

To evaluate the risk factors for PEP, several baseline patient characteristics and the treatment profile were compared between the PEP (n=13) and no-PEP group (n=134). Age [PEP and no-PEP, 85 (range: 77-98) and 81 (range: 46-99) years, respectively; p=0.0246] and the rectal administration of diclofenac [PEP and no-PEP, 3 (23.1%) and 71 (53.0%) patients, respectively; p=0.0460] were identified as risk factors for PEP in the univariate analyses (Table 3). In the multivariate logistic regression analysis, age and the rectal administration of diclofenac were included to calculate the risk factors for PEP. The patients were divided into two groups according to the median age (81 years). The analysis revealed that the non-administration of rectal diclofenac (OR= 3.530; 95% CI=1.017-16.35; p=0.0468) was an independent risk factor for PEP (Table 4).

Discussion

In previous studies, the rectal administration of NSAIDs was found to be effective in preventing PEP (6, 7). In these meta-analyses, a 50-100-mg rectal dose of diclofenac or indomethacin prevented PEP; however, this dose is considered to have toxic effects on the gastric and renal functions. Moreover, the rectal administration diclofenac at a dose of 50 mg is considered too high for elderly patients or for patients with a low body weight. The toxic effects of NSAIDs have been reported to be dose-dependent (11, 12). Thus, if a 25-mg rectal dose of NSAIDs can prevent PEP, it is likely to be safer than a 50-mg dose.

Otsuka et al. evaluated the safety and efficacy of low-dose (25 or 50 mg) diclofenac in preventing PEP, in comparison to a non-administration group, in a randomized controlled

Table 3. The Univariate Analysis of the Risk Factors for PEP.

	PEP (n=13)	No PEP (n=134)	p value
Female, n (%)	8 (61.5%)	68 (50.8%)	0.566
Age (years), median (IQR)	85 (77-98)	81 (46-99)	0.0246*
BMI (kg/m²), median (IQR)	18.9 (15.9-28.0)	21.1 (10.2-33.2)	0.176
BSA (m²), median (IQR)	1.37 (1.08-1.91)	1.43 (1.00-2.34)	0.401
Billroth I reconstruction, n (%)	1 (7.7%)	2 (1.5%)	0.244
Billroth II reconstruction, n (%)	0 (0%)	3 (2.2%)	1.00
Biliary stone, n (%)	9 (69.2%)	84 (62.7%)	0.769
Cancer, n (%)	4 (30.8%)	50 (37.3%)	0.769
History of PEP, n (%)	1 (7.7%)	14 (10.5%)	1.00
First ERCP, n (%)	7 (53.9%)	67 (50.0%)	1.00
Difficult cannulation, n (%)	4 (30.7%)	22 (16.4%)	0.247
Pancreatography, n (%)	3 (23.1%)	30 (22.4%)	1.00
ES, n (%)	4 (30.7%)	62 (46.3%)	0.385
EPBD, n (%)	0 (0%)	4 (3.0%)	1.00
EPLBD, n (%)	0 (0%)	15 (11.2%)	0.363
Biliary stent placement, n (%)	7 (53.9%)	61 (45.5%)	0.577
Pancreatic stent placement, n (%)	0 (0%)	1 (0.8%)	1.00
Procedure duration (min), median (IQR)	30 (7-70)	22 (4-117)	0.907
Diclofenac, n (%)	3 (23.1%)	71 (53.0%)	0.0460*

*p<0.05. IQR: interquartile range, BMI: body mass index, BSA: body surface area, ERCP: endoscopic retrograde cholangiopancreatography, ES: endoscopic sphincterotomy, EPBD: endoscopic papillary balloon dilation, EPLBD: endoscopic papillary large balloon dilation, PEP: post-ERCP pancreatitis

Table 4. The Multivariate Analysis of the Risk Factors for PEP.

	Odds ratio	95% Confidence Interval	p value
Age (≥81 years)	1.882	0.5700-7.319	0.306
No rectal administration of diclofenac	3.530	1.017-16.35	0.0468*

*p<0.05. PEP: post-ERCP pancreatitis

study in Japan. They 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]. Furthermore, in multivariate logistic regression analysis, the non-administration of diclofenac was found to be a significant independent risk factor for PEP (OR=10.352; 95% CI=2.147-81.709; p=0.009). In Otsuka's study, a 50-mg rectal dose of diclofenac was administered; however, a 25-mg dose was administered to patients with a body weight of <50 kg. The results suggested that there was no significant difference in the incidence of PEP between patients who received 25-mg and 50-mg diclofenac [2/22 (9.1%) vs. 0/29 (0%), respectively; p=0.101] (9). Another retrospective study by Yoshihara et al. comparing the use of a 25-mg or 50-mg rectal dose of diclofenac to prevent PEP reported that the incidence of PEP in the 25-mg group was significantly higher than that in the 50-mg group [28/84 (33.3%) vs. 11/71 (15.5), respectively; p=0.018]; this result was also found using a multivariate analysis (OR=0.35; 95% CI=0.11-0.70; p=0.007) (13). However, this study had a limitation: the baseline patient characteristics, including sex, age, and BMI were not comparable between the 25-mg and 50-mg groups. Female sex and age were identified as risk factors for PEP (14, 15). In the study by Yoshihara et al., the BMI in the 25-mg group was significantly higher than that in the 50-mg group, which could have reduced the effect of the 25-mg dose.

In our study, the occurrence of PEP in the 25-mg rectal diclofenac group [3/74 (4.1%)] was significantly lower than that in the control group [10/73 (13.7%)]. The non-administration of a 25-mg rectal dose of diclofenac was an independent risk factor for the occurrence of PEP. There were no significant differences in the baseline patients' characteristics, especially sex, age, history of PEP, difficult cannulation, pancreatography, EPBD, and bile duct or pancreatic duct stenting, which are considered risk factors for PEP (14-17). Thus, a 25-mg rectal dose of diclofenac might prevent PEP; however, it remains unclear whether the effect of the 25-mg dose was less than that of the 50-mg dose, and further studies should be performed to elucidate this point.

The pathophysiology of PEP is not fully understood. It is suggested that the inflammatory response induced by ERCP causes irritation of the pancreatic duct and plays a critical role in the development of PEP (18, 19). NSAIDs can inhibit phospholipase A2, which is involved in the synthesis of pancreatic inflammatory mediators, such as leukotrienes,

platelet-activating factors, and prostaglandins via the arachidonic acid cascade (20). This is considered to be one of the mechanisms through which they prevent PEP. A concern with the administration of diclofenac is that it may mask abdominal pain, thus apparently masking PEP. However, it has been reported that the peak concentration of diclofenac is reached at 30 to 90 minutes after its rectal administration, and that 90% of the diclofenac dose is cleared within 3 to 4 hours after its administration (21, 22). In our study, we measured abdominal pain within 24 hours after the ERCP procedure to monitor for PEP. We would not expect the effect of rectal diclofenac to be sustained for this duration.

The severe adverse effects of NSAIDs include gastrointestinal hemorrhage, ulceration, and acute renal failure (8). The administration of a 50-mg rectal dose of diclofenac is not common for Japanese patients because the toxicities of NSAIDs are dose-dependent (11, 12, 23). In our study, no patients developed gastrointestinal hemorrhage, ulceration, or acute renal failure. Thus, the 25-mg rectal dose was considered to be acceptable before ERCP.

Our study is associated with some limitations. First, because of the retrospective design, there was a potential for selection bias. In the early study period, ERCP was more frequently performed without the administration of diclofenac. This might have improved the operator's technical skill during the latter period. However, ERCP with the administration of diclofenac became more popular later in the study period, although there were no significant differences in the baseline characteristics of the patients. Second, the prevention of PEP with NSAIDs has been previously reported; nevertheless, our study only investigated the use of diclofenac. Finally, the patients in the diclofenac group only received rectal diclofenac before ERCP. Puig et al. reported, in a systematic review, that NSAIDs were effective when administered either before or after ERCP (7). However, a 50-100-mg rectal dose of NSAIDs (diclofenac or indomethacin) was assessed in that systematic review, and it is unclear whether the administration of a 25-mg rectal dose after ERCP is also effective in preventing PEP.

In conclusion, a 25-mg rectal dose of diclofenac was considered to be effective in preventing PEP, and to show a favorable safety profile. Further studies are needed to confirm these findings.

The authors state that they have no Conflict of Interest (COI).

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