Intramuscular diclofenac for the prevention of post-ERCP pancreatitis: a randomized trial

Authors Se Woo Park[1], Moon Jae Chung[2], Tak Geun Oh[2], Jeong Youp Park[2], Seungmin Bang[2], Seung Woo Park[2], Si Young Song[2]

Institutions
[1] Department of Internal Medicine, Institute of Gastroenterology, Hallym University College of Medicine, Seoul, Korea
[2] Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author
Moon Jae Chung, MD
Department of Internal Medicine
Institute of Gastroenterology
Yonsei University College of Medicine
50 Yonsei-ro
Seodaemun-gu
Seoul 120-752
Korea
Fax: +82-2-3936884
mjchung@yuhs.ac

Background and study aims: Rectal nonsteroidal anti-inflammatory drugs have been shown to reduce the incidence of postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). The aim of this study was to determine whether intramuscular diclofenac reduces the risk of PEP.

Patients and methods: Patients who underwent ERCP were randomized to receive either 90 mg of diclofenac or placebo by intramuscular injection immediately after the procedure. PEP was defined as elevated serum amylase levels (at least three times the upper limit of normal 24 hours after the procedure) associated with new or worsened upper abdominal, epigastric, or back pain.

Results: In total, 380 patients were randomized, and 343 were eligible for analysis. The two groups were similar regarding clinical and demographic factors, as well as patient- and procedure-related risk factors for PEP. PEP developed in 20/170 patients (11.8 %) in the placebo group and in 22/173 patients (12.7 %) in the diclofenac group (P = 0.87). Multivariate regression analysis failed to illustrate that intramuscular diclofenac prevented PEP (odds ratio 0.79; 95 % confidence interval 0.39 – 1.25; P = 0.51).

Conclusion: Prophylactic intramuscular diclofenac had no beneficial preventive effect on PEP. Clinicaltrials.gov NCT01717599.

Introduction

Postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most frequent and serious complication of ERCP procedures, occurring in approximately 4 % of unselected patients and carrying high risks of morbidity and mortality [1]. Furthermore, the frequency of complications may approach 30 % or more depending on the presence of risk factors [2]. Pharmacological prophylaxis of PEP has been the topic of several investigations in recent years; however, chemoprevention of pancreatitis remains controversial.

Many pharmacological agents including nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated for their potential to reduce the risk of PEP. The proposed mechanism of prophylactic NSAIDs in the prevention of PEP is the inhibition of phospholipase A2, cyclooxygenase, and neutrophil-endothelial interactions, all of which are believed to play important roles in the pathogenesis of acute pancreatitis [3]. The results of several randomized, controlled trials and meta-analyses provide evidence of the efficacy of NSAIDs for reducing PEP [4 – 7]. The most recent meta-analysis [4] demonstrated that NSAIDs were associated with a lower risk of PEP in seven high-quality studies (relative risk 0.58; 95 % confidence interval [CI] 0.44 – 0.76; P < 0.001). Consequently, NSAIDs are the only drugs with proven efficacy for prophylaxis against PEP in the European Society of Gastrointestinal Endoscopy guidelines [8], although they are not mentioned in the American Society of Gastrointestinal Endoscopy or Japanese Society of Gastrointestinal Endoscopy guidelines [9]. The advantages of this prophylaxis are its low cost and the possibility of "on-demand" treatment. In addition, NSAIDs are easily administered, and they display a favorable risk profile when given as a single dose, making them an attractive option for preventing PEP.

The majority of clinical trials included in meta-analyses demonstrated the beneficial effects of only rectal administration of NSAIDs. To the best of our knowledge, there is only one small, prospective, placebo-controlled study [10] in which parenteral (intramuscular) diclofenac tended to prevent PEP in a subgroup analysis of patients without sphincter of Oddi dysfunction (SOD). This benefit did not extend to the whole group. Rectal indomethacin is more expensive than par-

enteral NSAIDs, and it is not readily available in Korea.
The aim of the current large-scale, randomized, double-blinded study was to determine whether prophylactic intramuscular diclofenac reduces the incidence and severity of PEP in patients undergoing ERCP.

Methods

Patients and study protocol

Between September 2012 and August 2013, consecutive patients older than 20 years who were scheduled to undergo diagnostic or therapeutic ERCP at the Yonsei University Medical Center were recruited for the study. Patients were excluded from study participation if they had hypersensitivity to diclofenac, recent peptic ulcer disease or active/recent gastrointestinal bleeding within 4 weeks, renal dysfunction (creatinine > 1.4 mg/dL), NSAID use during the preceding week (acetylsalicylic acid 325 mg daily or less was acceptable), acute pancreatitis during the 2 weeks before ERCP, a history of chronic pancreatitis, previous sphincterotomy, or if they refused to participate in the study. Patients with a confirmed pregnancy and those who were breastfeeding were also excluded. Furthermore, patients were excluded if they underwent ERCP on an outpatient basis, for procedures such as stone removal following previous sphincterotomy, change or removal of previous plastic biliary stents, or surveillance biopsy after endoscopic papillectomy without pancreatocholangiography, which are considered to carry minimal potential risks of PEP.
Patients were randomized using opaque, sealed envelopes containing random numbers assigning them to receive either a 90-mg intramuscular diclofenac bolus dose (given as a 2-mL ampule) immediately after ERCP (diclofenac group) or a 2-mL saline bolus only (placebo group). Randomization was performed in a blinded fashion by pharmacy staff using computer-generated random numbers. Physicians, investigators, and patients were unaware of the treatment allocation. The intramuscular route was selected on the basis of available small-scale data suggesting that intramuscular diclofenac is effective in preventing PEP, possibly due to more rapid and complete bioavailability than that achieved with oral administration [10].
The trial was designed as a single-center, randomized study. The study protocol was approved by the institutional review board of the ethics committee of Yonsei University School of Medicine, Seoul, Korea, before initiation of the study. All patients provided written informed consent before randomization. The trial is registered with Clinicaltrials.gov (NCT01717599).

ERCP procedure

All ERCP procedures were performed by four endoscopists (S.W.P., S.M.B., J.Y.P., and M.J.C.) who each had previously performed over 1000 ERCP procedures. ERCP was performed with patients under conscious sedation with propofol and pethidine, under monitoring by an anesthesiologist. Hyoscine-*n*-butyl (Buscopan; Boehringer Ingelheim Ltd., Bracknell, UK) was used as a smooth-muscle relaxant at the discretion of the endoscopist. Cannulation of the common bile duct (CBD) was attempted first with a conventional cannula (Conture ERCP cannula; Boston Scientific, Athens, Greece), either with a guidewire (guidewire-assisted cannulation) or without a guidewire (contrast-assisted cannulation). Contrast medium was injected only when selective deep cannulation was expected to be in the direction of the CBD. In cases where this was not accomplished, a straight hydrophilic-coated tip guidewire was used to aid cannulation. If the endoscopist failed after 5 minutes, a pull-type sphincterotome (Clever-cut; Olympus, Athens, Greece) was used for a further 5 minutes with or without a guidewire. No contrast medium was injected if the guidewire had not been previously advanced through the route that was considered, with confidence by the endoscopists, to be the CBD. A precut papillotomy was attempted if trials of wire-guided cannulation using a pull-type sphincterotome failed on the basis of the following criteria: cannulation time more than 5 minutes or unintentional pancreatic duct cannulation more than three times.
At the end of the procedure, the endoscopists recorded the presence of periampullary diverticula, total procedure time (defined as the time from the first radiograph taken immediately before insertion of the endoscope to the last radiograph taken immediately after withdrawal of the endoscope), time to deep cannulation of the CBD (defined as the time from the radiograph taken immediately before the initiation of cannulation to the radiograph taken immediately after successful cannulation), difficulty level of cannulation, extent of pancreatic opacification, biliary and/or pancreatic duct findings, and interventions such as endoscopic sphincterotomy, endoscopic papillary balloon dilation (EPBD), or stenting, if performed. Difficult cannulation was defined as more than eight attempts [11].
After the procedure, patients continued fasting until the next morning. Serum amylase levels were measured at baseline, and at 4 hours and 18 – 24 hours after the procedure. If the investigator determined that a patient did not have PEP, then the patient resumed a free oral diet. All patients underwent ERCP as inpatients.

Definitions and main outcome measures

The primary outcome of the study was the incidence of PEP, defined as follows [12]: serum amylase level at least three times the upper limit of the normal range (> 345 g/dL) plus newly developed or worsened pancreatic-type abdominal pain and tenderness with nausea and/or vomiting for more than 24 hours after ERCP. Once PEP occurred, patients received conservative treatment for acute pancreatitis. Specifically, PEP was graded as follows [12]: 1) mild, symptoms lasting 3 days or less and a mildly edematous appearance of the pancreas on ultrasonography and/or computed tomography (CT); 2) moderate, requiring specific therapeutic measures for 4 – 10 days after the procedure (Balthazar's grade B/C on CT); and 3) severe, local or systemic complications lasting longer than 10 days after the procedure (Balthazar's grade D/E), or death. CT findings that included the presence of either tissue necrosis involving more than 30 % of the pancreatic gland or peripancreatic fluid collection were also used to classify pancreatitis as severe.

Statistical analysis

Based on the findings from a previous preliminary study with intramuscular diclofenac [10], a group sample sizes of 171 in both the diclofenac and placebo groups would achieve 80 % power to detect a difference of 10 % between the group proportions. The proportion in the diclofenac group was assumed to be 17.5 % under the null hypothesis and 7.5 % under the alternative hypothesis. To allow for a suspected dropout rate of 10 %, 190 patients were required for each group.
Categorical variables were analyzed using the chi-squared test, as appropriate, and continuous variables were expressed as means with SDs and were analyzed using the Student's *t*-test. Risk

factors for PEP were examined by univariate and multivariate analyses and calculated with an odds ratio (OR) and 95 %CI using a logistic regression method. A *P* value of less than 0.05 was considered to be significant in all tests. Statistical analyses were performed using SPSS software for Windows, version 17 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

A total of 380 patients were initially enrolled and randomized into the diclofenac or placebo groups (**Fig. 1**). Among them, 37 patients were excluded after randomization because of noncompliance with the scheduled examinations. Three patients in the diclofenac group and six patients in the placebo group were excluded from the study because of unstable vital signs. The major papilla could not be reached in 26 patients (12 diclofenac, 14 placebo) because of anatomical alteration following previous surgery (e.g. subtotal gastrectomy with Billroth II reconstruction or total gastrectomy with Roux en Y reconstruction), significant duodenal stricture as a result of tumor infiltration, or an intradiverticular position. One patient in the diclofenac group did not undergo ERCP because no CBD stones were seen on endoscopic ultrasonography before ERCP. Another patient in the diclofenac group sustained a duodenal perforation during the ERCP, and required surgery; this patient was therefore excluded from the analysis. Thus, a total of 343 patients were eligible for analysis. In total, 173 patients received diclofenac (diclofenac group), and 170 patients received placebo (placebo group). Cannulation was successful in all of the 343 patients included in the analysis.

Table 1 shows the demographic, clinical, and endoscopic characteristics of the two groups. The groups did not differ in age, sex, body mass index, or the results of laboratory tests. In addition, the indications for ERCP did not differ between the two groups. The most common indication for ERCP was bile duct stones (51.9 %, 178/343), followed by malignant obstructive jaundice (35.9 %, 123/343). Endoscopic findings and treatment modalities during ERCP did not differ between the two groups. There were no significant differences between the two groups regarding the presence of periampullary diverticula, total procedure time, and selective deep cannulation time. Endoscopic sphincterotomy was conducted in 71.1 % (123/173) of patients in the diclofenac group and in 74.7 % (127/170) of those in the placebo group. Endoscopic insertion of a biliary stent was performed more frequently in the placebo group than in the diclofenac group, though the difference was not significant (47.6 % [81/170] vs. 38.7 % [67/173]; *P* = 0.095). Similarly, pancreatic duct stents were inserted in six patients in each group without a statistically significant difference.

PEP

The overall incidence of PEP was 12.2 % (42/343) (**Table 2**). It was graded as mild in 37 patients (10.8 %), moderate in 3 patients (0.9 %), and severe in 2 patients (0.6 %). All 42 patients recovered after conservative treatment. There was no significant difference between the two study groups in the rate of PEP (diclofenac group vs. placebo group: 22/173 [12.7 %] vs. 20/170 [11.8 %]; *P* = 0.87).

In subgroup analyses of widely known risk factors for PEP (female sex, normal bilirubin level, retrieval of CBD stones, EPBD, or pancreatic opacification), there was no significant reduction in the rate of PEP in the diclofenac group compared with that in the placebo group. An additional analysis of the primary outcomes was performed for the full intention-to-treat population of all randomized patients, by applying the following scenario to the missing data based on a previous report [11]: PEP occurred in all 20 excluded patients in the placebo group and nearly 50 % (8 patients) of the 17 excluded patients in the diclofenac group. There were no significant differences between the two groups regarding the incidence of PEP in the full intention-to-treat population (16.3 % in the diclofenac group vs. 21.1 % in the placebo group; *P* = 0.292).

Two cases of severe pancreatitis occurred in the diclofenac group. These patients were managed conservatively for 15 and 17 days, respectively. Furthermore, three cases of moderate pancreatitis occurred, including one patient in the diclofenac group and two patients in the placebo group. There were no procedure- or pancreatitis-related deaths in the study.

Risk factors associated with PEP

Potential patient- and procedure-related risk factors for PEP were analyzed. In addition, the influence of pharmacological prophylaxis on PEP was estimated. Variables that were potentially associated with the incidence of PEP are presented in **Table 3**. On univariate analysis, significant patient-related factors included male sex (for female sex compared with male sex: OR 0.359, 95 % CI 0.166 – 0.776; *P* = 0.009). Procedure-related risk factors included pancreatic sphincterotomy (OR 6.644, 95 %CI 1.932 – 22.847; *P* = 0.003), endoscopic papillectomy (OR 4.554, 95 %CI 1.047 – 19.801; *P* = 0.043), and placement of a pancreatic stent (OR 3.855, 95 %CI 1.108 – 13.414; *P* = 0.034). Furthermore, there was marginal significance regarding difficult biliary cannulation (OR 2.770, 95 %CI 0.944 – 8.133; *P* = 0.064), precut papillotomy (OR 1.961, 95 %CI 0.941 – 4.085; *P* = 0.072), and pancreatic opacification (OR 1.961, 95 %CI 0.993 – 3.871; *P* = 0.052). Of the aforementioned risk factors, multivariate logistic regression analysis identified male sex (for female sex compared with male sex: OR 0.350, 95 %CI 0.154 – 0.794; *P* = 0.012) and EPBD (OR 3.443, 95 % CI 1.176 – 10.075; *P* = 0.024) as independent risk factors for PEP. In addition, there was marginal significance for pancreatic sphincterotomy (OR 7.040, 95 %CI 0.937 – 52.909; *P* = 0.058) and endoscopic papillectomy (OR 6.546, 95 %CI 0.843 – 50.840; *P* = 0.072).

Tolerability and safety assessment

Bleeding after endoscopic sphincterotomy was observed in 21 of 250 patients (8.4 %). All bleeding was mild oozing that occurred during the procedure. No cases of massive delayed bleeding occurred. All bleeding episodes, including 12 (9.4 %) in the placebo group and 9 (7.3 %) in the diclofenac group (*P* = 0.507), were self-limited and were controlled completely during endoscopy without special hemostatic intervention. The serum creatinine values, which are indicative of renal failure, were estimated for each group before and after ERCP. The overall mean difference in serum creatinine levels between baseline and 1 day after treatment was significantly different in both the diclofenac group (0.88 ± 0.32 vs. 0.80 ± 0.25; *P* = 0.001) and the placebo group (0.85 ± 0.36 vs. 0.79 ± 0.25; *P* = 0.018). Five patients (four diclofenac, one placebo) had creatinine levels > 1.4 mg/dL following the administration of diclofenac or placebo, with no significant difference between the groups (*P* = 0.371). There was one major complication (immediate duodenal perforation) in the diclofenac group. The patient was treated with primary surgical closure, and experienced a relatively acceptable postoperative clinical course with regres-

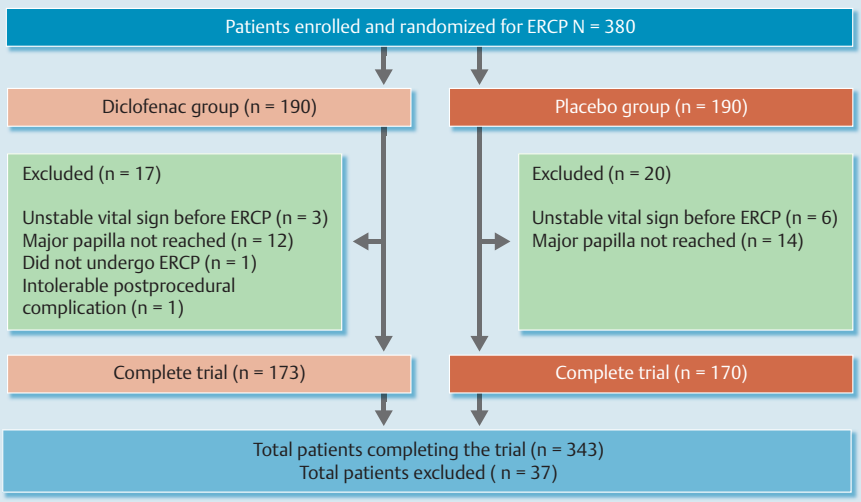

Fig. 1 Flow of patients through the study.

Table 1 Baseline characteristics of patients.

Characteristics	Diclofenac (n = 173)	Placebo (n = 170)	*P* value
Age, mean ± SD, years	63.94 ± 12.93	64.93 ± 13.71	0.493
Sex, male, %	106 (61.3)	98 (57.6)	0.494
BMI, mean ± SD, kg/m^2	23.99 ± 2.91	23.12 ± 2.84	0.395
Pre-ERCP laboratory tests, mean ± SD			
WBC, /mm^3	7966.42 ± 4436.36	7646.76 ± 3708.49	0.470
Amylase, g/dL	58.12 ± 32.59	56.64 ± 31.10	0.668
Lipase, g/dL	44.65 ± 45.89	47.51 ± 50.81	0.585
Total bilirubin, mg/dL	3.20 ± 4.22	3.84 ± 5.63	0.231
r GPT, IU/L	367.79 ± 314.24	395.40 ± 390.29	0.471
ALP, IU/L	211.34 ± 188.98	195.62 ± 169.87	0.419
AST, IU/L	94.64 ± 119.93	100.58 ± 133.47	0.665
ALT, IU/L	103.38 ± 111.90	124.57 ± 183.93	0.197
Main indication for ERCP, n (%)			
Malignant obstructive jaundice	58 (33.5)	65 (38.2)	0.556
Benign obstructive jaundice	23 (13.3)	15 (8.8)	
Suspected/known bile duct stone	90 (52.0)	88 (51.8)	
Other	2 (1.2)	2 (1.2)	
Periampullary diverticulum, n (%)	54 (31.2)	43 (25.3)	0.224
Procedure time, mean ± SD, minutes	17.65 ± 9.90	16.91 ± 9.59	0.486
Cannulation			
Bile duct cannulation time, mean ± SD, minutes	4.79 ± 5.37	4.35 ± 4.79	0.426
Total cannulation attempts, mean ± SD	2.90 ± 2.36	2.66 ± 1.97	0.314
Difficult cannulation, n (%)[1]	11 (6.4)	8 (4.7)	0.504
Precut papillotomy, n (%)	33 (19.1)	30 (17.6)	0.733
Pancreatic acinarization	92 (53.2)	88 (51.8)	
Pancreatic duct injection frequency, mean ± SD	0.76 ± 0.85	0.76 ± 0.89	0.937
Pancreatic duct injection degree, n (%)			
to head	48 (27.7)	48 (28.2)	0.833
to body	33 (19.1)	28 (16.5)	
to tail	11 (6.4)	12 (7.1)	
Pancreatic sphincterotomy, n (%)	3 (1.7)	8 (4.7)	0.118
EPBD, mean ± SD			
Degree of EPBD, mmHg	10.85 ± 1.31	10.81 ± 1.63	0.931
Duration of EPBD, seconds	37.50 ± 9.80	37.86 ± 11.64	0.915
Endoscopic sphincterotomy, n (%)	123 (71.1)	127 (74.7)	0.452
Papillectomy, n (%)	5 (2.9)	3 (1.8)	0.490
Biliary stent, n (%)	67 (38.7)	81 (47.6)	0.095
Pancreatic stent, n (%)	6 (3.5)	6 (3.5)	0.494

BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; r GPT, r-glutamyl transpeptidase ; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; EPBD, endoscopic papillary balloon dilation.
Categorical variables are presented as n (%) and were compared between groups using chi-squared tests unless otherwise stated. Continuous variables are presented as mean ± SD and were compared using Student's *t* test.
[1] Difficult cannulation was defined as >8 attempts.

Table 2 Incidence and severity of post-endoscopic retrograde cholangiopancreatography pancreatitis in the two study groups and subgroup analysis.

Characteristics, n (%)	Diclofenac (n = 173)	Placebo (n = 170)	*P* value
All patients			
Total patients	173 (100)	170 (100)	
PEP	22 (12.7)	20 (11.8)	0.870
Severity			
Mild	19 (11.0)	18 (10.6)	0.608
Moderate	1 (0.6)	2 (1.2)	
Severe	2 (1.2)	0 (0)	
Female patients			
Total patients	67 (100)	72 (100)	
PEP	6 (9.0)	3 (4.2)	0.313
Normal bilirubin			
Total patients	72 (100)	76 (100)	
PEP	6 (8.3)	9 (11.8)	0.590
CBD stones			
Total patients	90 (100)	88 (100)	
PEP	7 (7.8)	8 (9.1)	0.793
Malignant obstruction			
Total patients	58 (100)	65 (100)	
PEP	11 (19.0)	9 (13.8)	0.473
EPBD			
Total patients	20 (100)	21 (100)	
PEP	2 (10.0)	5 (23.8)	0.410
Pancreatic opacification			
Total patients	92 (100)	88 (100)	
PEP	15 (16.3)	13 (14.8)	0.839

PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; CBD, common bile duct; EPBD, endoscopic papillary balloon dilation.

sion of abdominal pain. Furthermore, no patients complained of muscle pain during the injection, and all administrations were tolerated to completion.

Discussion

Endoscopists have long grappled with PEP, which is the most frequent and threatening complication of ERCP. Multiple risk factors including patient-related risk factors (i.e. young age, female sex, history of PEP) have been elucidated in several recent, large-scale studies from Europe and the United States [13–15]. Endoscopists have evaluated many mechanical procedures and pharmacological prophylactic solutions for the prevention of PEP. In particular, several recent meta-analyses demonstrated that the use of NSAIDs as pharmaco-prophylactic agents reduces the incidence and severity of PEP [4–6]. In a meta-analysis by Ding et al. [6] including 10 randomized controlled trials, the relative risk for PEP development after prophylactic NSAID use was 0.57 (95 %CI 0.38–0.86). Subgroup analysis of six studies [11,16–20] using rectal NSAIDs revealed significant efficacy (relative risk 0.42, 95 %CI 0.31–0.58; $P < 0.001$) without heterogeneity. Only one study [10] has examined the use of intramuscular NSAIDs for the prevention of PEP, and results demonstrated that parenteral diclofenac had no overall benefit on the prevention of pancreatitis. However, parenteral diclofenac did reduce the incidence of PEP in patients without SOD. These results contrast those of the current study, which demonstrated no significant reduction in the incidence of PEP with intramuscular diclofenac prophylaxis (univariate OR 0.915, 95 %CI 0.480–1.747; multivariate OR 0.790, 95 %CI 0.391–1.252). The current study showed that the incidence of PEP was 12.2 % (42/343) in the overall study sample, which was not higher than the previously reported incidence rate [11], in spite of dealing with more difficult cases such as altered anatomy, history of cannulation failure at other hospitals, and, most commonly, large difficult CBD stones. The primary aim of the current study was to assess the consistency of our experience with that of a previous study [10], which demonstrated a relationship between intramuscular diclofenac and PEP in patients without SOD who underwent ERCP. Although there were no patients diagnosed with SOD in the current study, intramuscular diclofenac did not display any benefit for the prophylaxis of PEP.

Other risk factors for PEP were evaluated in the current study, and EPBD (OR 3.443, 95 %CI 1.176–10.075; $P = 0.024$) was found to be a significant independent risk factor for PEP on multivariate analysis, in accordance with a previous study [15]. Male sex was also an independent risk factor for PEP, which was inconsistent with the findings of several reports [15,21]. Despite being identified as significant risk factors for PEP in univariate analysis, pancreatic sphincterotomy, endoscopic papillectomy, and placement of a pancreatic stent were not significant factors in multivariate analysis. Indeed, many randomized, controlled trials and meta-analyses [22–24] revealed that pancreatic stents have a definite beneficial role in preventing PEP in high-risk patients. However, in the current study, the risk of PEP was higher in patients who underwent pancreatic stent placement in univariate analysis. This finding could be explained by the fact that the placement of pancreatic stents was usually attempted in patients considered at high risk for developing PEP.

The mechanisms of ERCP-induced pancreatic injury are not clearly understood, and several proposed factors may act independently or in combination to induce PEP. Irrespective of the mechanism of injury, the host inflammatory response to endoscopic instrumentation appears to play an important role in the pathophysiology of PEP [25]. A delay of several hours (median 4.5 hours) exists between pancreatic injury during ERCP and the onset of symptoms [25]. This "therapeutic window" invites the use of anti-inflammatory strategies to modulate the premature intracellular activation of proteolytic enzymes and acinar cell damage, and subsequent local inflammatory response that in turn leads to the release of chemokines and pro-inflammatory cytokines into the general circulation [26]. In terms of effective agents for preventing PEP, NSAIDs potently inhibit phospholipase A2, which is implicated as an important player in the initial inflammatory cascade of acute pancreatitis [27,28].

Diclofenac is an NSAID marketed worldwide in oral, suppository, transdermal patch, gel, and intramuscular formulations. The parenteral route is often preferred due to its more rapid onset of action compared with other routes [29]. The peak concentration of parenteral diclofenac occurs approximately 30 minutes after injection, and the elimination half-life of plasma is 1.5 hours [30]. All three previous studies [16,18,20] assessing rectally administered diclofenac to prevent PEP had positive results or demonstrated a trend toward positivity, whereas the overall results of one published study [10] assessing intramuscularly administered diclofenac were negative, as in the current study. Summarizing the available evidence, the rectal route of diclofenac administration appears effective for preventing PEP. However, it remains uncertain whether the route of diclofenac administration affects the clinical efficacy.

Table 3 Univariate and multiple regression analysis of factors associated with post-endoscopic retrograde cholangiopancreatography pancreatitis.

Factors, n (%)	No PEP (n = 301)	PEP (n = 42)	Univariate OR (95 %CI)	*P*	Multivariate OR (95 %CI)	*P*
Age, years						
<60	87 (28.9)	17 (40.5)	1		1	
≥60	214 (71.1)	25 (59.5)	0.598 (0.308 – 1.162)	0.129	0.536 (0.258 – 1.114)	0.095
Sex						
Male	171 (56.8)	33 (78.6)	1		1	
Female	130 (43.2)	9 (21.4)	0.359 (0.166 – 0.776)	0.009	0.350 (0.154 – 0.794)	0.012
BMI						
Normal	226 (75.1)	33 (78.6)	1		1	
Overweight	65 (21.6)	9 (21.4)	0.948 (0.432 – 2.083)	0.895	0.734 (0.298 – 1.808)	0.502
Obese	10 (3.3)	0 (0)				
Diverticulum						
No	215 (71.4)	31 (73.8)	1		1	
Yes	86 (28.6)	11 (26.2)	0.887 (0.427 – 1.844)	0.748	0.854 (0.369 – 1.977)	0.854
Cannulation						
Easy	287 (95.3)	37 (88.1)	1		1	
Difficult[1]	14 (4.7)	5 (11.9)	2.770 (0.944 – 8.133)	0.064	1.738 (0.486 – 6.220)	0.395
Precut papillotomy						
No	250 (83.1)	30 (71.4)	1		1	
Yes	51 (16.9)	12 (28.6)	1.961 (0.941 – 4.085)	0.072	1.740 (0.681 – 4.446)	0.247
Pancreatic duct injection						
No	149 (49.5)	14 (33.3)	1		1	
Yes	152 (50.5)	28 (66.7)	1.961 (0.993 – 3.871)	0.052	1.140 (0.493 – 2.638)	0.759
Pancreatic sphincterotomy						
No	295 (98.0)	37 (88.1)	1		1	
Yes	6 (2.0)	5 (11.9)	6.644 (1.932 – 22.847)	0.003	7.040 (0.937 – 52.909)	0.058
EPBD						
No	267 (88.7)	35 (83.3)	1		1	
Yes	34 (11.3)	7 (16.7)	1.571 (0.647 – 3.811)	0.318	3.443 (1.176 – 10.075)	0.024
Endoscopic sphincterotomy						
No	83 (27.6)	10 (23.8)	1		1	
Yes	218 (72.4)	32 (76.2)	1.218 (0.573 – 2.589)	0.608	1.420 (0.521 – 3.872)	0.493
Papillectomy						
No	296 (98.3)	39 (92.9)	1		1	
Yes	5 (1.7)	3 (7.1)	4.554 (1.047 – 19.801)	0.043	6.546 (0.843 – 50.840)	0.072
Biliary stent						
No	176 (58.5)	19 (45.2)	1		1	
Yes	125 (41.5)	23 (54.8)	1.704 (0.890 – 3.263)	0.108	1.854 (0.899 – 3.825)	0.095
Pancreatic stent						
No	293 (97.3)	38 (90.5)	1		1	
Yes	8 (2.7)	4 (9.5)	3.855 (1.108 – 13.414)	0.034	0.798 (0.088 – 7.252)	0.841
Intramuscular diclofenac						
No	150 (49.8)	20 (47.6)	1		1	
Yes	151 (50.2)	22 (52.4)	0.915 (0.480 – 1.747)	0.788	0.790 (0.391 – 1.252)	0.511

BMI, body mass index; EPBD, endoscopic papillary balloon dilation.
[1] Difficult cannulation was defined as > 8 attempts.

None of the study patients in either group had clinical suspicion of SOD, which has been a well-recognized risk factor for PEP in previous studies. The incidence of SOD in Korea is much lower than that in Western countries. In a previous study conducted in Korea, Kim et al. found that the incidence of SOD among 3372 patients who underwent ERCP over a 5-year period was only 0.5 % (16/3372) [31]. Furthermore, the diagnostic "gold-standard" for SOD varies, and thus, there are several potential sources of bias in the diagnosis of SOD in previous studies. Therefore, we do not consider SOD to be a risk factor for PEP.

The current study appeared to be underpowered due to some study limitations. The lack of an observed preventive benefit could be attributed to a Type II error, as there was insufficient power to detect a true preventive benefit. Adjustment for many baseline confounding factors may by itself dilute the potential preventive benefit of diclofenac. In addition, the primary analysis targeted patients for whom data regarding the primary end point could be obtained, rather than the usual intention-to-treat group. However, a conservative analysis of all randomized patients matched the primary analysis.

In conclusion, the current study illustrated that a single dose of prophylactic intramuscular diclofenac does not reduce the rate of PEP, even in high-risk groups. Large-scale, comparative, multicenter, randomized, controlled trials are needed to confirm these findings before final conclusions can be drawn.

Competing interests: None

References

1 *Andriulli A*, *Loperfido S*, *Napolitano G* et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol 2007; 102: 1781 – 1788
2 *Freeman ML*, *Guda NM*. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc 2004; 59: 845 – 864
3 *Makela A*, *Kuusi T*, *Schroder T*. Inhibition of serum phospholipase-A2 in acute pancreatitis by pharmacological agents in vitro. Scand J Clin Lab Invest 1997; 57: 401 – 407
4 *Yuhara H*, *Ogawa M*, *Kawaguchi Y* et al. Pharmacologic prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: protease inhibitors and NSAIDs in a meta-analysis. J Gastroenterol 2014; 49: 388 – 399
5 *Elmunzer BJ*, *Waljee AK*, *Elta GH* et al. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. Gut 2008; 57: 1262 – 1267
6 *Ding X*, *Chen M*, *Huang S* et al. Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: a meta-analysis. Gastrointest Endosc 2012; 76: 1152 – 1159
7 *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 – 16
8 *Dumonceau JM*, *Andriulli A*, *Deviere J* et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. Endoscopy 2010; 42: 503 – 515
9 *Anderson MA*, *Fisher L*. ASGE Standards of Practice Committee. et al. Complications of ERCP. Gastrointest Endosc 2012; 75: 467 – 473
10 *Senol A*, *Saritas U*, *Demirkan H*. Efficacy of intramuscular diclofenac and fluid replacement in prevention of post-ERCP pancreatitis. World J Gastroenterol 2009; 15: 3999 – 4004
11 *Elmunzer BJ*, *Scheiman JM*, *Lehman GA* et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012; 366: 1414 – 1422
12 *Cotton P*, *Lehman G*, *Vennes J* et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991; 37: 383 – 393
13 *Loperfido S*, *Angelini G*, *Benedetti G* et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc 1998; 48: 1 – 10
14 *Masci E*, *Toti G*, *Mariani A* et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol 2001; 96: 417 – 423
15 *Freeman ML*, *DiSario JA*, *Nelson DB* et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 2001; 54: 425 – 434
16 *Otsuka T*, *Kawazoe S*, *Nakashita S* et al. Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a randomized controlled trial. J Gastroenterol 2012; 47: 912 – 917
17 *Montano LozaA*, *Rodriguez LomeliX*, *Garcia CorreaJE* et al. [Effect of the administration of rectal indomethacin on amylase serum levels after endoscopic retrograde cholangiopancreatography, and its impact on the development of secondary pancreatitis episodes]. Rev Esp Enferm Dig 2007; 99: 330 – 336
18 *Murray B*, *Carter R*, *Imrie C* et al. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology 2003; 124: 1786 – 1791
19 *Sotoudehmanesh R*, *Khatibian M*, *Kolahdoozan S* et al. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol 2007; 102: 978 – 983
20 *Khoshbaten M*, *Khorram H*, *Madad L* et al. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol 2008; 23: e11 – 16
21 *Masci E*, *Mariani A*, *Curioni S* et al. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. Endoscopy 2003; 35: 830 – 834
22 *Singh P*, *Das A*, *Isenberg G* et al. Does prophylactic pancreatic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials Gastrointest Endosc 2004; 60: 544 – 550
23 *Sofuni A*, *Maguchi H*, *Itoi T* et al. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. Clin Gastroenterol Hepatol 2007; 5: 1339 – 1346
24 *Mazaki T*, *Masuda H*, *Takayama T*. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: a systematic review and meta-analysis. Endoscopy 2010; 42: 842 – 853
25 *Messmann H*, *Vogt W*, *Holstege A* et al. Post-ERP pancreatitis as a model for cytokine induced acute phase response in acute pancreatitis. Gut 1997; 40: 80 – 85
26 *Karne S*, *Gorelick FS*. Etiopathogenesis of acute pancreatitis. Surg Clin North Am 1999; 79: 699 – 710
27 *Diaz-Gonzalez F*, *Sanchez-Madrid F*. Inhibition of leukocyte adhesion: an alternative mechanism of action for anti-inflammatory drugs. Immunol Today 1998; 19: 169 – 172
28 *Gross V*, *Leser HG*, *Heinisch A* et al. Inflammatory mediators and cytokines – new aspects of the pathophysiology and assessment of severity of acute pancreatitis? Hepatogastroenterology 1993; 40: 522 – 530
29 *Zeitlinger M*, *Rusca A*, *Oraha AZ* et al. Pharmacokinetics of a new diclofenac sodium formulation developed for subcutaneous and intramuscular administration. Int J Clin Pharmacol Ther 2012; 50: 383 – 390
30 *Shep D*, *Ojha A*, *Patel S* et al. Comparative bioavailability study of a new formulation of injection of 75 mg diclofenac sodium in 1 ml with the conventional injection of 75 mg diclofenac sodium given in 3 ml volume. Curr Clin Pharmacol 2011; 6: 26 – 29
31 *Kim MH*, *Lee SK*, *Chang YH* et al. The clinical characteristics of 16 patients with sphincter of Oddi dyskinesia. Korean J Gastrointest Endosc 1996; 16: 585 – 590