J Gastroenterol (2012) 47:912–917
DOI 10.1007/s00535-012-0554-7

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a randomized controlled trial

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Received: 8 September 2011 / Accepted: 25 January 2012 / Published online: 18 February 2012

Abstract
Background Acute pancreatitis is a common complication of endoscopic retrograde cholangiopancreatography (ERCP). Rectal nonsteroidal anti-inflammatory drugs (specifically, 100 mg of diclofenac or indomethacin) have shown promising prophylactic activity in post-ERCP pancreatitis (PEP). However, the 100-mg dose is higher than that ordinarily used in Japan.
Methods We performed a prospective randomized controlled study to evaluate the efficacy of low-dose rectal diclofenac for the prevention of PEP. Patients who were scheduled to undergo ERCP were randomized to receive a saline infusion either with 50 mg of rectal diclofenac (diclofenac group) or without (control group) 30 min before ERCP. The dose of diclofenac was reduced to 25 mg in patients weighing <50 kg. The primary outcome measure was the occurrence of PEP.
Results Enrollment was terminated early because the planned interim analysis found a statistically significant intergroup difference in the occurrence of PEP. A total of 104 patients were eligible for this study; 51 patients received rectal diclofenac. Twelve patients (11.5%) developed PEP: 3.9% (2/51) in the diclofenac group and 18.9% (10/53) in the control group ($p = 0.017$). After ERCP, the incidence of hyperamylasemia was not significantly different between the two groups. Post-ERCP pain was significantly more frequent in the control group than in the diclofenac group (37.7 vs. 7.8%, respectively; $p < 0.001$). There were no adverse events related to diclofenac.
Conclusions Low-dose rectal diclofenac can prevent PEP.

Keywords ERCP · NSAIDs · Complication · Prevention · Meta-analysis

Abbreviations

ERCP	Endoscopic retrograde cholangiopancreatography
NSAIDs	Nonsteroidal anti-inflammatory drugs
PEP	Post-ERCP pancreatitis

Introduction

Acute pancreatitis is an important complication after endoscopic retrograde cholangiopancreatography (ERCP). Generally, post-ERCP pancreatitis (PEP) occurs in 1–10% of patents [1–4]. Nevertheless, most patients develop mild or moderate pancreatitis; severe pancreatitis requiring further intervention or leading to death occurs in 0.3–0.6% of patients [2–5]. Numerous mechanical and pharmacological procedures have been evaluated for the prevention of PEP; however, the results of pharmacological interventions have been generally disappointing.

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In some randomized controlled trials [6–9] and a meta-analysis [10] of these trials, rectal nonsteroidal anti-inflammatory drugs (NSAIDs) showed promising prophylactic activity in PEP. The rectal NSAID dose used in these trials was 100 mg of diclofenac or indomethacin, which is higher than the normal single dose used in Japan. For these reasons, we conducted a prospective randomized controlled trial to evaluate the efficacy of low-dose rectal NSAIDs for the prevention of PEP.

Methods

Study design

Patients who were scheduled to undergo ERCP were included. Patients were excluded if they had acute or active pancreatitis, chronic pancreatitis with acute painful exacerbation, a history of endoscopic sphincterotomy, peptic ulcer diseases, rectal diseases, aspirin-induced asthma, NSAIDs during the preceding 1 week, hypersensitivity to NSAIDs, treatment with triamterene (contraindicated with diclofenac), severe renal dysfunction, or were pregnant or breast-feeding.

Patients were randomly assigned to receive either 50 mg of rectal diclofenac with saline infusion 30 min before ERCP (diclofenac group) or saline infusion only (control group). The dose of diclofenac was reduced to 25 mg in patients whose body weight was <50 kg. Although treatment with antibiotics and sedatives was allowed, the use of protease inhibitors, octreotide, or any other agents aiming to decrease the risk of pancreatitis was not permitted.

Treatment group allocation was blinded to the endoscopists and the investigator. At the end of the procedure, the endoscopists recorded difficulty of cannulation, findings of the biliary and/or pancreatic duct, and interventions such as sphincterotomy, papillary balloon dilation, and stenting, if performed. The difficulty of cannulation was graded as follows: easy cannulation, defined as that within 5 attempts; moderately difficult cannulation, defined as 6 to 15 attempts; difficult cannulation, defined as >15 attempts; and abandonment of cannulation [2]. Oral intake of water was allowed throughout the observation period. If the investigator determined that a patient did not have PEP, the patient resumed a free oral diet. All patients underwent ERCP on admission.

This trial was designed as a multicenter, prospective, randomized study. The study protocol was approved by the institutional review board of each participating institution before initiation of the study. All patients provided written informed consent before randomization. This trial is registered with the University Hospital Medical Information Network Clinical Trial Registry, no. UMIN000004658.

Study endpoints

The primary outcome measure was the occurrence of PEP, defined by the criteria of Cotton et al. [1] as the development of abdominal pain and elevation of the serum amylase level to greater than three times the upper normal limit within 24 h after ERCP. The severity of PEP was graded according to the duration of therapeutic intervention for PEP [1]. Mild PEP required 2–3 days; moderate PEP required 4–10 days; and severe PEP required >10 days, necessitated surgical or intensive treatment, or contributed to death. Secondary endpoints were hyperamylasemia, defined as serum amylase levels of more than three times the upper normal limit within 24 h after ERCP; post-ERCP pain, defined as new or worsened abdominal pain after ERCP; and diclofenac toxicity. Serum amylase was measured before ERCP and any time the patients complained of pain within 24 h after ERCP; otherwise, it was routinely measured 24 h after ERCP.

Statistical analyses

The initially planned sample size was 230 patients from 2 participating sites. This sample size was calculated to provide a one-sided test with 80% power to detect 65% risk reduction [10] with an alpha error of 0.05. We assumed that the incidence of PEP in the control group would be 15% (estimated from the preceding 2-year data in our institutions). To demonstrate the preventive effect of rectal diclofenac on PEP, a two-by-two table and χ^2 test were used. The Mann–Whitney *U*-test was used for the comparison of continuous variables. Univariate and multivariate logistic regression analyses were performed to identify factors associated with PEP. The planned duration of accrual was 3 years. The interim analysis was planned for 2 years after initiation of this study with adjustment for multiple comparisons taken into account by the Lan-DeMets method [11]. The O'Brien-Fleming type alpha spending function was used. Data analyses were performed using R version 2.12.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Enrollment and discontinuation

Enrollment in the study began in March 2009. The planned interim analysis, performed in February 2011, found a significant difference in the occurrence of PEP between the two groups with adjustment by the alpha spending function. Therefore, enrollment was discontinued and the study was terminated in February 2011.

Demographics

Between March 2009 and February 2011, 155 ERCP procedures were performed. A total of 104 patients were eligible for this study; 51 patients received rectal diclofenac (Fig. 1). The groups were similar with regard to indications for ERCP (Table 1). There were no statistically significant differences between the groups regarding factors that might increase the risk of PEP [2, 3, 12], except for sex (Table 2). According to the protocol, 22 patients in the diclofenac group received a dose of 25 mg. Median body weight was not significantly different between the groups: 55 kg in the diclofenac group and 53 kg in the control group ($p = 0.708$). No patients underwent precut sphincterotomy, papillary balloon dilation, or pancreatic stent placement.

Outcomes of study endpoints

Of all the patients, 11.5% (12/104) developed PEP: 3.9% (2/51) in the diclofenac group and 18.9% (10/53) in the control group. The incidence of PEP was significantly lower in the diclofenac group ($p = 0.017$). PEP was mild in both affected patients in the diclofenac group. In the control group, on the other hand, the severity of PEP was mild in 7 patients and moderate in 3 patients (Table 3). Forty-two patients in the diclofenac group and 39 patients in the control group had biliary stones (Table 1). Stone removal was attempted for all patients with biliary stones. However, complete removal was not achieved on the first attempt in seven patients in the diclofenac group and seven patients in the control group. Of these 14 patients, two in the control group developed PEP. Sixty-four patients underwent sphincterotomy: 32 patients in the diclofenac group and 32 patients in the control group. The incidence of PEP in the sphincterotomized patients was lower in the diclofenac group (2/32; 6.3%) than in the control group (7/32; 21.9%), although the difference was not statistically significant. Likewise, the incidence of PEP in the patients who received 25 mg of rectal diclofenac was lower (2/22; 9.1%) than that in the control group patients whose body weight was <50 kg (4/21; 19.0%); however, this difference was not significant. On multivariate logistic regression analysis, allocation to the control group was a significant independent risk factor for PEP development (Table 4).

After ERCP, hyperamylasemia was observed in 16 patients (31.4%) in the diclofenac group and 19 patients (35.8%) in the control group ($p = 0.629$). Twenty-four patients had post-ERCP pain, including patients with PEP. The incidence of post-ERCP pain was significantly higher in the control group than in the diclofenac group (37.7 vs. 7.8%, respectively; $p < 0.001$). There were no adverse events related to diclofenac (Table 3). The cost per dose of diclofenac was JPY 62.3 and 76.4 for 25 and 50 mg, respectively.

Discussion

In a previous meta-analysis, prophylactic rectal NSAIDs were effective in preventing PEP [10]. Four randomized

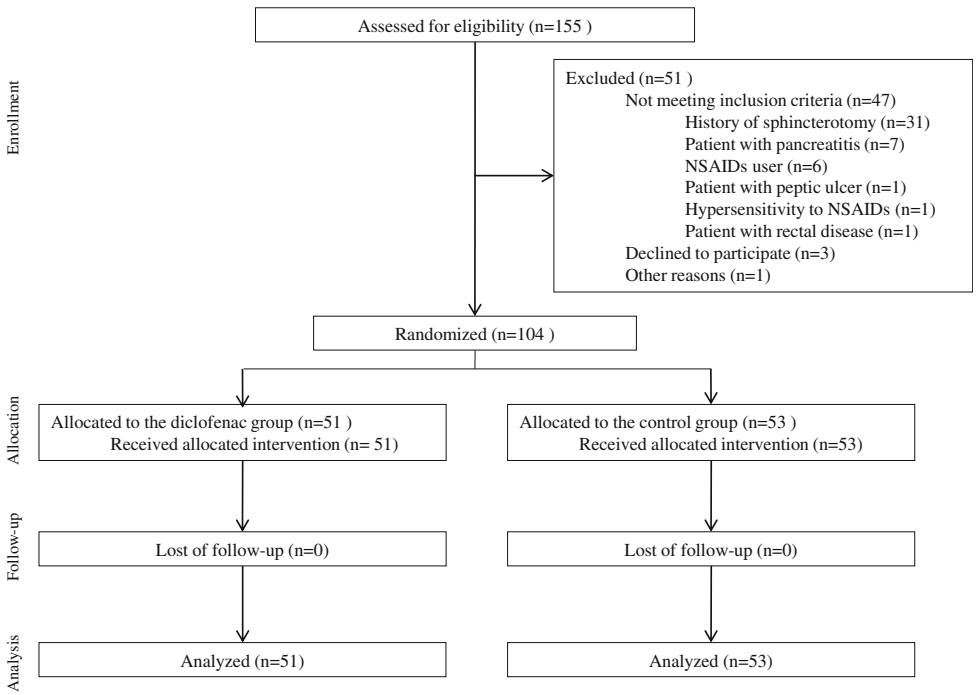

Fig. 1 Flow diagram of the study

Table 1 Indications for endoscopic retrograde cholangiopancreatography (ERCP) in the diclofenac and control groups

	Diclofenac group ($n = 51$)	Control group ($n = 53$)
Biliary stone	42	39
Biliary tract cancer	3	8
Intraductal papillary mucinous neoplasms	4	2
Pancreatic cancer	0	2
Others	2	2

There were no statistically significant differences between the groups

Table 2 Risk factors for post-ERCP pancreatitis in the diclofenac and control groups

	Diclofenac group ($n = 51$)	Control group ($n = 53$)	p
Female	31	20	0.019
Age, years, median	75	72	0.675
History of post-ERCP pancreatitis	1	1	0.978
Difficult cannulation[a]	23	20	0.446
Small bile duct (<10 mm)	30	29	0.674
Diagnostic pancreatography	4	4	0.955
Biopsy or cytology	5	4	0.684
Sphincterotomy	32	32	0.804
Biliary stent placement	0	2	0.163

ERCP endoscopic retrograde cholangiopancreatography

[a] Difficult cannulation includes moderately difficult and difficult cannulation as described in the "Methods"

Table 3 Summary of outcome measures

Outcome	Diclofenac group	Control group	p
Post-ERCP pancreatitis			
All patients (%)	2/51 (3.9)	10/53 (18.9)	0.017
Mild pancreatitis	2/2	7/10	
Moderate pancreatitis	0/2	3/10	
Sphincterotomized patients (%)	2/32 (6.3)	7/32 (21.9)	0.072
Body weight <50 kg (%)	2/22 (9.1)	4/21 (19.0)	0.352
Hyperamylasemia (%)	16/51 (31.4)	19/53 (35.8)	0.629
Post-ERCP pain (%)	4/51 (7.8)	20/53 (37.7)	<0.001
Adverse events related to diclofenac	0	–	

ERCP endoscopic retrograde cholangiopancreatography

controlled trials [6–9] were included in the meta-analysis; all adopted a 100-mg dose of rectal diclofenac or indomethacin. However, 100 mg of rectal NSAIDs is almost 2- to 4-fold the single dose usually given in Japan, and it is not approved. The efficacy of NSAIDs, including diclofenac, is reportedly dose-dependent [13]. Our study suggests that even low-dose rectal NSAIDs exert prophylactic activity against PEP. A meta-analysis of the five randomized trials, including the present study, was performed. The fixed effects meta-analysis for PEP had no statistical heterogeneity in the present group ($p = 0.59$). The result showed a Mantel–Haenszel pooled relative risk for PEP with prophylactic rectal NSAID administration of 0.30 (95% confidence interval, 0.18–0.49) (Fig. 2). The pooled number of patients needed to treat with rectal NSAIDs to prevent one episode of PEP was 11.

Although several hypotheses exist about the mechanism of PEP, it is suggested that the patient's inflammatory reaction to irritation of the pancreatic duct plays a critical role [14–16]. NSAIDs have potent activities in inhibiting phospholipase A_2, which is implicated as an important player in the initial inflammatory cascade of acute pancreatitis by regulating proinflammatory mediators such as prostaglandins, leukotrienes, and platelet-activating factors [17]. Although many agents have been evaluated for the prevention of PEP, the results of most of these trials were disappointing. Some promising results have been shown with gabexate and somatostatin [18, 19]; however, these drugs are expensive and are not commercially available worldwide. Rectal NSAIDs are inexpensive, globally available, easily administered, and have a very good safety profile. There were no adverse events related to rectal diclofenac in our study. The toxicities of NSAIDs are also dose-dependent [20–22]. Because physicians in Japan sometimes hesitate to administer 50 mg of rectal diclofenac to patients with low body weights, we chose a 25-mg dose of rectal diclofenac. The incidence of PEP in our patients receiving 25 and 50 mg diclofenac was 9% (2/22) and 0% (0/29), respectively, showing no statistically significant difference ($p = 0.101$). The peak concentration of diclofenac is reached between 30 and 90 min after rectal administration. The elimination half-life is 2 h, and 90% of the drug is cleared within 3–4 h after administration [13, 23]. A concern of diclofenac use in regard to the evaluation of PEP is that the agent may mask abdominal pain. However, based on the above data, it is unlikely that the analgesic effect of rectal diclofenac is sustained for a long time.

Our study had some limitations. First, this study design was not blinded to the patients; however, the endoscopists and the investigator were masked to the treatment allocation. Further study using placebo is warranted. Second, the ratio of females to males was not comparable between the two study groups. Female sex is identified as a risk factor for PEP [2, 3]. However, although the diclofenac group included more female patients than did the control group, the incidence of PEP was lower in the diclofenac group. Finally, the overall incidence of PEP in our study was

Table 4 Univariate and multivariate analyses for identification of independent risk factors for post-ERCP pancreatitis

Variables	Univariate		Multivariate	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Female	2.279 (0.669–9.030)	0.203		
Younger age (<70 years)	1.476 (0.408–5.012)	0.534		
History of post-ERCP pancreatitis	4.400 (0.560–25.760)	0.110		
Difficult cannulation[a]	0.679 (0.171–2.321)	0.551		
Small bile duct (<10 mm)	1.608 (0.471–6.371)	0.463		
Diagnostic pancreatography	1.104 (0.056–7.091)	0.930		
Biopsy or cytology	0.955 (0.049–5.971)	0.967		
Sphincterotomy	2.018 (0.559–9.547)	0.316		
Control group	5.698 (1.404–38.420)	0.030	10.352 (2.147–81.709)	0.009

OR odds ratio, *95% CI* 95% confidence interval, *ERCP* endoscopic retrograde cholangiopancreatography

[a] Difficult cannulation includes moderately difficult and difficult cannulation as described in the "Methods"

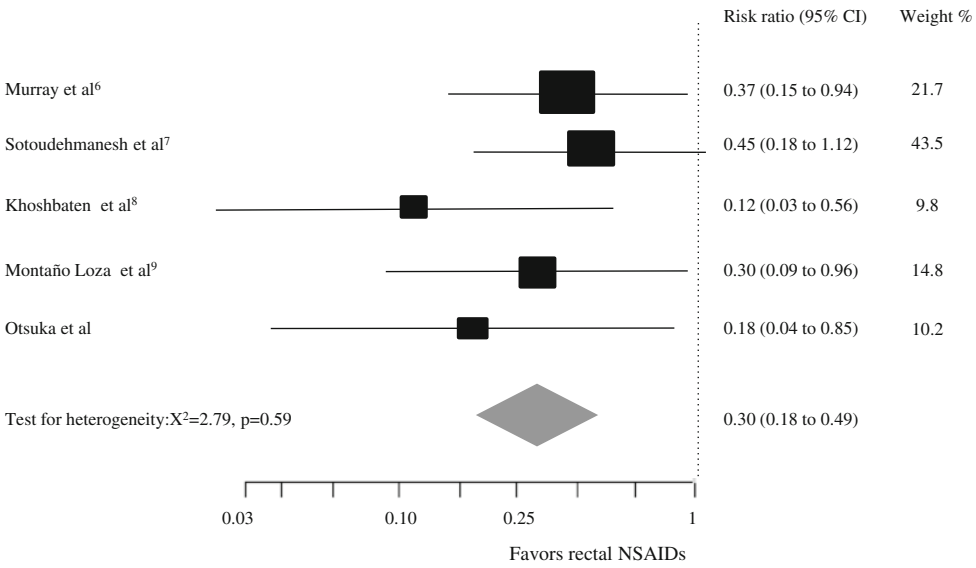

Fig. 2 Meta-analysis of five trials, including the present study (Otsuka et al.), of prophylactic rectal nonsteroidal anti-inflammatory drugs (NSAIDs) for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis

11.5% (3.9% in the diclofenac group and 18.9% in the control group). While the incidence of PEP is generally 1–10% of patients, it sometimes reaches ≥25% depending on the presence of risk factors [24]. In our study, the rate of PEP and difficult cannulation cases was high in spite of the "low-risk" population with a high rate of biliary stone cases. One reason for this high incidence of PEP is that our institutions are low-volume centers that perform ERCP in approximately 40 patients annually. There are two specialists in each hospital; however, trainees conduct many procedures because our hospitals are educational institutions for endoscopy. Another reason is that not using the wire-guided cannulation technique might affect the PEP rate [25]. In these conditions, however, low-dose rectal diclofenac reduces the risk of PEP.

In conclusion, this randomized trial shows that low-dose rectal diclofenac can prevent PEP. This simple and safe method is recommended for patients who undergo ERCP.

Acknowledgments The authors would like to thank Professor Kazuma Fujimoto (Department of Internal Medicine, Saga Medical School) for his excellent advice.

Conflict of interest The authors declare that they have no conflict of interest.

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