Low-dose rectal diclofenac does not prevent post-ERCP pancreatitis in low- or high-risk patients

Short title: Low-dose rectal diclofenac does not prevent PEP

Takao Katoh[1], Kousaku Kawashima[2], Nobuhiko Fukuba[3], Shigeto Masuda[1], Hiroko Kobatake[1], Kosaku Masaki[1], Yasuhiro Araki[1], Koichiro Kawano[1], Katsuhisa Nishi[1], Mamoru Takenaka[4], Shunji Ishihara[2], and Yoshikazu Kinoshita[2, 5]

[1]Department of Gastroenterology, Hyogo Prefectural Awaji Medical Center, 137-1 Shioya, Sumoto, Hyogo 656-0021, Japan
[2]Department of Internal Medicine II, Shimane University Faculty of Medicine 89-1, Enya-cho, Izumo, Shimane 693-8501, Japan
[3]Department of Internal Medicine, Izumo City General Medical Center 613, Nadabun-cho, Izumo, Shimane 691-0003, Japan
[4]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan
[5]Steel Memorial Hirohata Hospital, 3-1 Yumesaki-cho, Hirohata-ku, Himeji, Hyogo 671-1122, Japan.

Correspondence to:
Takao Katoh, MD
Department of Gastroenterology, Hyogo Prefectural Awaji Medical Center
137-1 Shioya, Sumoto, Hyogo 656-0021, Japan
Tel: +81-799-22-1200; Fax: +81-853-20-2187
Email: takao.k@juno.ocn.ne.jp

Financial support:
No funding declared.

Declaration of conflict of interest:

Yoshikazu Kinoshita has received honoraria from Astellas Pharma Inc, Astra Zeneca K.K., Otsuka Pharmaceutical Co., Ltd., ZERIA Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mylan EPD G.K., EA Pharma Co., Ltd., ABBOTT JAPAN Co., Ltd., Eisai Co., Ltd., Sucampo Pharma, LLC.

Author contributions:

Study design: Katoh T and Kinoshita Y.

Writing manuscript: Katoh T, Kawashima K, Fukuba N, Ishihara S, and Kinoshita Y.

Acquisition of data: Katoh T, Masuda S, Kobatake H, Masaki K, Araki Y, Kawano K, Nishi K, and Takenaka M.

Manuscript preparation: Katoh T, Kawashima K, Fukuba N, Ishihara S, and Kinoshita Y.

Statistical analysis: Katoh T.

Supervisor of study: Kinoshita Y.

Abstract

Background and Aim:

The most common adverse event following an endoscopic retrograde cholangiopancreatography (ERCP) procedure is post-ERCP pancreatitis (PEP). Rectal nonsteroidal anti-inflammatory drug (NSAID) administration has shown promise to reduce the risk of PEP in high-risk patients. However, in contrast to high-risk patients, the role of NSAID administration in patients with low risk remains controversial.

Methods:

We performed a prospective, single-center, single-blinded, two arm parallel-group, randomized controlled trial to clarify the efficacy of low dose (50 mg) rectal NSAID administration for preventing PEP in at-risk patients. Patients scheduled to undergo ERCP were randomized into 2 groups, those with and without rectal administration of diclofenac. Patients in the diclofenac group received 50 mg of rectal diclofenac 30 minutes before undergoing ERCP. The primary endpoint was rate of PEP.

Results:

A total of 303 were randomized into the study groups. Four patients declined participation following randomization and another 2 were withdrawn. As a result, a total of 147 patients were assigned to the diclofenac group and 150 to the control group. The baseline and procedural characteristics were similar in both groups. The primary endpoint of PEP occurrence was seen in 13 of 297 patients (4.4%), including 8 (5.4%) in the diclofenac group and 5 (3.3%) in the control group (P=0.286). Additionally, those results were not significantly different when patients were classified as low or high risk.

Conclusions:

Prophylactic low-dose rectal diclofenac did not reduce the incidence of PEP following ERCP in patients classified as low or high risk.

Keywords: diclofenac, ERCP, post-ERCP pancreatitis.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is important for biliopancreatic diagnostic and therapeutic procedures. However, management of the various complications that can occur following ERCP remains a major challenge for endoscopists, with the most common being post-ERCP pancreatitis (PEP). Several patient- and procedure-related risk factors have been identified to be associated with PEP, including young age, female gender, prior PEP, and sphincter of Oddi dysfunction (SOD), each of which is associated with a 15-20% increase in risk of PEP development [1.2].

Standard methods for preventing PEP can be classified into mechanical and pharmacological approaches. Recently, results of randomized controlled trials of rectal nonsteroidal anti-inflammatory drug (NSAID) administration and prophylactic pancreatic stent placement have shown promise for reducing the risk of PEP in high-risk patients [3, 4]. Additionally, several meta-analyses have found that prophylactic rectal NSAID administration reduces the risk of PEP [5]. On the other hand, various other studies have recently reported a lack of beneficial effect of NSAID treatment for preventing PEP [6]. Different from high-risk patients, the role of NSAID administration in patients with low risk remains controversial.

Most past studies that examined the effects of prophylactics on PEP used diclofenac or indomethacin, with no difference found between them [7, 8], thus we used diclofenac in the present investigation. Several studies conducted in western countries have presented results showing that a prophylactic rectal NSAID administration with a 100-mg dose reduced the risk of PEP. However, NSAID side-effects are dose dependent [9] and the physical stature of Japanese people is generally smaller as compared to individuals from western nations. Therefore, a dose of 50 mg is generally prescribed by Japanese doctors and studies conducted in Japan have suggested beneficial effects of a 50-mg dose of diclofenac for preventing PEP [10]. Therefore, diclofenac at 50 mg was also used in this study.

In the present study, we attempted to clarify the efficacy of a rectal NSAID administration at a low dose (50 mg) for prevention of PEP in patients who underwent an ERCP procedure, including those with risk of PEP. In addition, the efficacy of pancreatic duct stenting for preventing PEP was also evaluated in high-risk patients.

Methods

Study design

This was a prospective, single-center, single-blinded, two arm parallel-group, randomized controlled trial. Approximately 400 ERCP procedures are performed annually at our institution by 3 experienced endoscopists and 6 trainees. The study protocol was approved by the institutional review-board of Hyogo Prefectural Awaji Medical Center and registered as a randomized controlled trial with the University Hospital Medical Information Network (registration number UMIN000031705). The participants were randomized using a blocked randomization scheme with randomly permuted block sizes to determine administration of diclofenac.

Patients

Patients over 15 years old and scheduled to undergo ERCP were enrolled. Those with active acute pancreatitis, contraindicated for NSAID therapy (severe renal dysfunction or active peptic ulcer disease), aspirin-induced asthma, NSAID allergy, rectal disease, or pregnant or breast feeding were excluded. In addition, patients with a regular intake of aspirin and/or other nonsteroidal anti-inflammatory drug (NSAID) were also excluded. Eligible patients were randomized into those with rectal diclofenac administration (diclofenac group) or without that treatment (control group).

The serum concentration of diclofenac given as a rectal suppository peaks at 30-90 minutes after administration [11], and several recent studies have demonstrated that rectal NSAID administration prior to ERCP is more effective for reducing the occurrence of PEP as compared to following ERCP [12, 13, 14]. Patients in the present diclofenac group received 50 mg of rectal diclofenac at 30 minutes before ERCP, with that amount reduced to 25 mg in those weighing less than 50 kg. All patients received a lactate supplement sodium solution (1500 mL) that was intravenously administered before and after ERCP, as well as a protease inhibitor (gabexate-mesilate, 0.3 mg/body weight) and prophylactic antibiotic administration (sulbactam/cefoperazone, 2 g/day) for 2 days. Endoscopists who performed ERCP for the present cohort were blinded to the patient randomization, which was decided by physicians who did not participated in the endoscopic procedures. Nurses administered rectal diclofenac at the ward prior to the ERCP procedure. Any administration of diclofenac was noted in the medical chart of

the patient only after the ERCP examination, thus the endoscopists had not opportunity to confirm patient grouping until after ERCP.

Pancreatic duct stent placement

Patients considered to have high risk for PEP, including cases investigated or treated by pancreatic duct brush cytology, or with a precut sphincterotomy, difficult cannulation, pancreatic duct guidewire, or endoscopic pancreatic sphincterotomy, underwent prophylactic pancreatic duct stenting. All stents used in the present study were sized 5 Fr.

Outcomes

The primary study endpoints were rate and severity of PEP. Pancreatitis was defined based on criteria presented by Cotton [15], and diagnosed in patients with development of upper-abdominal pain and an increased serum amylase concentration greater than 3 times over the upper limit of normal within 24 hours after ERCP. The severity of PEP was graded as mild (2-3 days required for recovery), moderate (4-10 days required for recovery), and severe (more than 10 days required for recovery). The secondary endpoint was the concentration of hyperamylasemia. Serum amylase was measured before ERCP, and again 2 and 24 hours after the procedure. Pancreatic-type amylase was measured at the same time. Hyperamylasemia was defined as 3 times over the upper limit of the normal range. In addition, we analyzed after dividing into subgroups based on risk. The high risk group was defined based on the presence of at least one of the following patient- or procedure-related risk factors. Patient-related factors included sphincter of Oddi dysfunction, age less than 50 years old and female gender, history of recurrent pancreatitis, and history of PEP. Procedure-related risk factors included difficult cannulation (cannulation duration ≥10 minutes), total procedure time ≥40 minutes, pancreatic sphincterotomy, pancreatic brush cytology, pancreatic injection ≥3 times, and pancreatic guidewire passage [2-4, 16]. Accordingly, patients without any risk factors were classified into the non-high risk group.

Statistical methods

The necessary sample size for the present study was estimated based on the reported incidence of PEP in previous studies [14, 15]. That incidence rate was predicted to be 16%, based on previous findings showing that NSAID administration prevents PEP. The value of NSAID administration was considered to be clinically important when the incidence of PEP was reduced to 70% of the level in the control group. It was estimated that the rate of incidence in the diclofenac group was reduced to 5% and the sample size was calculated, with an α error of 0.05 and β error of 0.80, to be 121 patients in each group based on these considerations.

For analysis, a chi-squared test, Fisher's exact test, and logistic regression analysis were used, as appropriate. In addition, statistical analysis of the effect of each risk factor on preventing the effects of NSAID treatment was also performed. Statistical analyses were performed using R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Between August 4, 2015 and June 30, 2018, ERCP-related procedures were performed in 616 patients with pancreatobiliary disease at Hyogo Prefectural Awaji Medical Center. Randomization for the trial was done with 303 of those patients who provided written informed consent and met the inclusion criteria. Four patients withdrew after randomization, thus a total of 299 were enrolled. Subsequently, 2 patients were found to have gastric outlet obstruction and were withdrawn. Thus, a total of 147 patients were allocated to the diclofenac group and 150 patients to the control group (Fig. 1).

The baseline characteristics of the enrolled patients were similar in both groups (Table 1). The mean (± standard deviation) age was 74.2 ± 12.2 years, and there were 177 (59.6%) males and 120 (40.4%) females, with only 17 (5.7%) classified as young (<50 year). Sixteen (5.4%) patients had recurrent pancreatitis and 4 (1.3%) a history of PEP. There were few cases with patient-related risk factors. Intraductal papillary mucinous neoplasms had a higher rate of incidence in the diclofenac group as compared to the control group, while the rates of previous sphincterotomy and chronic pancreatitis were lower in both groups as compared with those in a previous report [6].

Procedural characteristics are shown in Table 2. There were no differences regarding the rates of difficult cannulation, precut sphincterotomy, pancreatic duct procedure, biliary and pancreatic duct stenting, and previous biliary sphincterotomy between the groups. The rate of endoscopic biliary stone removal in the control group was significantly higher. The baseline and procedural characteristics were similar in both groups.

Study outcomes

The primary endpoint of PEP occurred in 13 (4.4%) of the 297 patients, including 8 (5.4%) of 147 in the diclofenac group and 5 (3.3%) of 150 in the control group (P=0.286) (Fig. 2). The incidence of PEP in the 2 groups was not significantly different. All patients with PEP underwent 30 days of follow-up examinations to assess the severity of pancreatitis. Severe or moderately PEP was found to occur in 2, 1 (0.7%) in the diclofenac group and 1 (0.6%) in the control group (P=0.646). All patients with

PEP were discharged within 30 days after ERCP. There were no statistical differences of incidence and severity of PEP between the two groups. Low-dose diclofenac did not reduce the incidence of PEP and did not improve the severity of PEP.

Hyperamylasemia was observed in 42 (14.1%) patients, 19 (12.9%) in the diclofenac group and 23 (15.3%) in the control group (P=0.618). There was no statistically significant difference between the groups in regard to the frequency of hyperamylasemia and low-dose diclofenac did not reduce the frequency of hyperamylasemia. Twenty-three (7.7%) of all patients had solely pancreatic-type hyperamylasemia, none of whom developed PEP.

Subgroup analysis

Patient-related risk factors for PEP revealed in univariate analysis are shown in Table 3. There was no statistically significant patient-related risk factor found in this study. As for procedural related risk factors, total procedural time, difficult cannulation, and biliary sphincterotomy were shown to be risk factors for PEP in univariate analysis, while multivariate analysis revealed long total procedural time statistically significant risk factors for PEP development.

Pancreatic duct stent placement (PSP) was performed for 52 (17.5%) of the 297 enrolled patients (Table 4). We compared that subgroup of patients with or without NSAID administration. Although there was no statistically significant difference, the rate of PEP occurrence in the diclofenac group (11.5%) tended to be higher than that in the control group (0%), including in cases treated by stent placement (P=0.235). In patients who did not receive pancreatic stent placement, the incidence of PEP was nearly the same regardless of the presence or absence of diclofenac (4.1% vs 4.0%).

As shown in Table 5, the high risk group was comprised of 171 patients (57.6%) and the non-high risk group (low risk) of 126 patients (42.4%). PEP was noted in 12 (7.0%) in the high risk group and 1 (0.8%) in the non-high risk group, while hyperamylasemia was observed in 39 (22.8%) and 3 (2.4%), respectively. Among the high risk group cases, few cases (11.8%) had patient-related risk factors, while most (98.8%) showed procedure-related risk factors.

The effects of diclofenac were investigated in both the high and non-high risk groups. Among patients in the high risk group, PEP was noted in 8 (9.3%) of 86 in the

diclofenac subgroup and 4 (4.7%) of 85 in the control group (P=0.37), indicating no significant difference in regard to the incidence of PEP in the high risk group. As for the non-high risk group, 0 (0%) of 61 patients in the diclofenac subgroup and 1 (1.5%) of 65 in the control group had PEP (P=1.00), again showing no difference for the incidence of PEP in non-high risk patients who underwent an ERCP procedure. Our results indicated that low-dose diclofenac did not reduce the incidence of PEP occurrence regardless of level of risk.

We also analyzed differences of incidence of PEP between patients administered diclofenac at 50 mg (n=119) and 25 mg (n=28). The incidence of PEP in those subgroups was 5.0% and 7.4%, respectively (P=0.648), indicating no statistically significant difference between those doses in regard to PEP incidence (data not shown).

Discussion

The findings of the present study indicate that a rectal administration of low-dose (50 mg) diclofenac in patients with low- or high PEP risk does not prevent occurrence of PEP, which is in contrast to several recent studies, though many of those excluded patients with low risk of PEP development [5, 16]. The Guidelines of the European Society of Gastrointestinal Endoscopy and Japanese Society of Hepato-Biliary-Pancreatic Surgery recommend routine rectal administration of an NSAID for all patients undergoing ERCP to prevent PEP [17, 18]. Nevertheless, recent studies have suggested that prophylactic rectal NSAID administration does not reduce the incidence of PEP in patients considered to have a low level of risk [6]. Furthermore, the Guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) do not recommend NSAID use for preventing PEP [19].

We considered that one of the reasons why NSAID administration was not found to be effective in the present cohort was because of the characteristics of the enrolled patients. In previous analyses of various types of NSAIDs, mainly patients with a high risk for developing PEP, such as those with SOD, were enrolled [5, 12, 20]. In contrast, patients with low as well as high risk of PEP occurrence were included in the present cohort. Our results showed that NSAID administration did not prevent PEP regardless of level of risk, possibly because very few of the enrolled patients had patient-related risk factors for PEP occurrence. In fact, a previous meta-analysis of mainly patients with low risk also found no beneficial effect of an NSAID for prevention of PEP [21].

Another possible reason for lack of beneficial effect of NSAID treatment in our study is the lower dose of diclofenac given. In nearly all related studies performed in western countries, the dose of diclofenac was 100 mg, different from that of the present study (50 mg). Previous studies conducted in Japan have suggested a beneficial value of a 50- or 25-mg dose of diclofenac. However, those were retrospective in design, had a small number of participants, or were performed at a center with a low volume of ERCP cases [10, 22]. Therefore, the quality of the present prospective randomized large scale study performed at a high volume center is considered to be superior.

A third possible reason to explain our findings is routine employment of pancreatic stent placement following an ERCP procedure for patients with high risk of

PEP. Such stent placement has already been confined to be effective for preventing PEP in cases with higher PEP. Thus, in the present cohort, a pancreatic stent was routinely used for those with higher patient- or procedure-related PEP risk, and the incidence of PEP was decreased. We consider that co-utilization of pancreatic stent placement with NSAID administration may have concealed the preventive effect of diclofenac.

Few studies of patients administered low-dose NSAID have been presented, thus the evidence level as compared to a 100-mg dose is low. Furthermore, in the present cohort, low-dose diclofenac did not reduce the incidence of PEP or frequency of hyperamylasemia. We also examined PEP incidence after dividing the patients into high risk and non-high risk groups, though incidence was not different between them. None of the present cases were considered appropriate for examination of the relationship of prophylactic administration with PEP occurrence. However, previous reports [2, 5, 16] have found that cases of PEP with high risk patient-related factors may be appropriate for diclofenac administration for PEP prophylaxis prior to ERCP. As for our finding of no difference in incidence of PEP in the present non-high risk group, we consider that this result was related to the low incidence of PEP regardless of usage of diclofenac.

In univariate analysis, factors associated with the incidence of PEP were shown to be longer procedure time, longer cannulation time. In multivariate analysis, that risk factor was longer total procedure time. Therefore, administration of low-dose diclofenac for prevention of PEP is considered to be inappropriate for high risk patients with procedure-related risk factors, especially difficult cannulation, and those with an extended procedure time as well as non-high risk patients. On the other hand, stratification of risk reduced the number of cases for analysis and we consider that large-scale studies are necessary in the future.

This study has some limitations, including performance in a single center with a single blinded design. Furthermore, most of the enrolled patients were elderly, though that is a reflection of the recent aging trend in Japanese society. Also, the dose of diclofenac given was lower than that in western studies. Finally, we overestimated the occurrence of PEP in the control group to be 16% based on past trials of PEP prevention by NSAID treatment, while the actual incidence of PEP was much lower in our results. A future study with a large population is necessary to confirm the present findings. Based on our results, we concluded that a low dose of prophylactic rectal diclofenac

does not reduce the incidence of PEP in patients undergoing ERCP who have a low level of risk.

In conclusion, prophylactic low-dose rectal diclofenac did not reduce the incidence of PEP following ERCP in patients with low or high risk. Administration of low-dose diclofenac for prevention of PEP seems to be inappropriate for low risk cases.

References

1. Kochar B, Akshintala VS, Afghani E, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. Gastrointest Endosc. 2015; 81: 143-149.
2. Freeman ML. Pancreatic stents for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Clin Gastroenterol Hepatol. 2007; 5: 1354-65.
3. Choudhary A, Bechtold ML, Arif M, et al. Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review. Gastrointest Endosc. 2011; 73: 275-82.
4. Mazaki T, Masuda H, Takayama T. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: a systematic review and meta-analysis. Endoscopy. 2010; 42: 842-53.
5. Sethi S, Sethi N, Wadhwa V, Garud S, Brown A. A meta-analysis on the role of rectal diclofenac and indomethacin in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Pancreas. 2014; 43: 190-7.
6. Levenick JM, Gordon SR, Fadden LL, et al. Rectal Indomethacin Does Not Prevent Post-ERCP Pancreatitis in Consecutive Patients. Gastroenterology. 2016; 150: 911-7.
7. Puig I, Calvet X, Baylina M, et al. How and when should NSAIDs be used for preventing post-ERCP pancreatitis? A systematic review and meta-analysis. PLoS One. 2014 Mar 27; 9: e92922.
8. Giagoudakis G, Markantonis SL. Relationships between the concentrations of prostaglandins and the nonsteroidal antiinflammatory drugs indomethacin, diclofenac, and ibuprofen. Pharmacotherapy. 2005; 25: 18-25.
9. Rostom A, Goldkind L, Laine L. Nonsteroidal anti-inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients. Clin Gastroenterol Hepatol. 2005; 3: 489-98.
10. 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: 912-7.

11. Sotoudehmanesh R, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol. 2007; 102: 978-83.
12. Sun HL, Han B, Zhai HP, Cheng XH, Ma K. Rectal NSAIDs for the prevention of post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. Surgeon. 2014; 12: 141-7.
13. Ding X, Chen M, Huang S, Zhang S, Zou X. Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: a meta-analysis. Gastrointest Endosc. 2012; 76: 1152-9.
14. Rustagi T, Njei B. Factors Affecting the Efficacy of Nonsteroidal Anti-inflammatory Drugs in Preventing Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Systematic Review and Meta-analysis. Pancreas. 2015; 44: 859-67.
15. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc. 1991; 37: 383-93.
16. 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: 1414-22.
17. Dumonceau JM, Andriulli A, Elmunzer BJ, et al; European Society of Gastrointestinal Endoscopy. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. Endoscopy. 2014; 46: 799-815.
18. Yokoe M, Takada T, Mayumi T, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci. 2015; 22: 405-32.
19. ASGE Standards of Practice Committee, Chandrasekhara V, Khashab MA, Muthusamy VR, et al. Adverse events associated with ERCP. Gastrointest Endosc. 2017; 85: 32-47.
20. Yaghoobi M, Rolland S, Waschke KA, et al. Meta-analysis: rectal indomethacin for the prevention of post-ERCP pancreatitis. Aliment Pharmacol Ther. 2013; 38: 995-1001.

21. Inamdar S, Han D, Passi M, Sejpal DV, Trindade AJ. Rectal indomethacin is protective against post-ERCP pancreatitis in high-risk patients but not average-risk patients: a systematic review and meta-analysis. Gastrointest Endosc. 2017; 85: 67-75.
22. Okuno M, Shiroko J, Taguchi D, et al. The Effectiveness of the Rectal Administration of Low-dose Diclofenac for the Prevention of Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis. Intern Med. 2018; 57: 2289-2294.

Figure legends

Fig. 1. Enrollment. Exclusion criteria are described in the Methods section. Renal dysfunction was defined as serum creatinine level >1.4 mg/dl. Contraindicated for NSAID treatment: active peptic ulcer (n=1), aspirin allergy (n=1). Others: bile duct injury and pancreatic duct injury as a result of traffic accident trauma.
Gastric outlet obstruction was only defined for cases in which the endoscope could not reach the papilla due to such an obstruction.

Fig. 2. Primary endpoints.

The comparison of rates of post-ERCP pancreatitis (PEP) and severity of pancreatitis. Eight (5.4%) of 147 in the diclofenac group and 5 (3.3%) of 150 in the control group developed PEP (P=0.286). Severe or moderate PEP occurred in 2 in patients, 1 (0.7%) in the diclofenac group and 1 (0.6%) in the control group (P=0.646).