Intravenous injection of low-dose flurbiprofen axetil for preventing post-ERCP pancreatitis in high-risk patients: An interim analysis of the trial

Yuji Fujita, Sho Hasegawa, Yuri Kato, Ken Ishii, Akito Iwasaki, Takamitsu Sato, Yusuke Sekino, Kunihiro Hosono, Atsushi Nakajima, Kensuke Kubota

Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, Yokohama, Japan

Introduction

Acute pancreatitis is the most common adverse event (AE) associated with endoscopic retrograde cholangiopancreatography (ERCP). Post-ERCP pancreatitis (PEP) occurs in 1% to 10% of patients [1–3], and in 17% to 40% of high-risk patients [4–6]. Most cases of PEP are mild or moderate, but severe pancreatitis, including that requiring endoscopic intervention, occurs in 0.4% to 0.6% of those cases [7,8]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are inhibitors of phospholipase A2, which is believed to have a pivotal role in the initial inflammatory cascade of acute pancreatitis [9–11]. Several randomized controlled trials [12–15] have confirmed the efficacy of rectal NSAIDs for prevention of PEP. However, in those studies, diclofenac or indomethacin was used at a dose of 100mg, which is higher than the usual dose in Asia; furthermore, rectal administration may be considered complicated. Intravenous injection of NSAIDs is technically easy for patients. It is desirable to minimize the dose of NSAIDs because of potent side effects [6]. Therefore, we conducted a randomized controlled clinical trial to evaluate the efficacy and safety of intravenous injection of low-dose flurbiprofen axetil for preventing PEP in high-risk patients.

Patients and methods

Study design

This study was prospective, randomized, and placebo-controlled. It was approved by the Institutional Review Boards before initiation of the study, and was registered (ClinicalTrials.gov, ID UMIN000011322).

Patients

Patients who were scheduled to undergo ERCP were included. All patients had a PEP risk score of ≥1 in a previous study [6,16] (Table 1). Patients were excluded for any of the following reasons: (1) acute or active pancreatitis; (2) metallic stent inserted across the papilla; (3) history of endoscopic sphincterotomy; (4) peptic ulcer diseases; (5) aspirin-induced asthma; (6) NSAIDs during the
preceding 1 week; (7) hypersensitivity to NSAIDs; (8) pregnancy or breastfeeding; (9) severe renal dysfunction; or (10) patients whom the doctor in attendance judged to be unsuitable for inclusion. Patients were randomly assigned to receive intravenous (IV) injection of 50 mg flurbiprofen axetil with 20 mL saline (flurbiprofen group), or IV injection of 20 mL saline only (placebo group). The dose of flurbiprofen axetil was reduced to 25 mg in patients whose body weight was <50 kg. Flurbiprofen axetil was injected IV immediately after ERCP while a patient was still in the procedure room. All patients received antibiotics (Sulbactam/Ampicillin 1g×2) and protease inhibitor (10 mg nafamostat mesilate). Randomization was performed using a random number table. Endoscopists and patients were blinded to the treatment group allocation. A total of 100 patients were randomized. ERCP was performed by 3 skilled endoscopists who each perform 200 to 300 ERCP procedures annually. We used a 15-degree backward-oblique angle duodenoscope with an elevator function (JF-260V, TJF-260V; Olympus Medical Systems Corp, Tokyo, Japan). After the duodenal papilla had been viewed from the front, selective cannulation was attempted using a conventional catheter (PR-104Q-1; Olympus) by contrast-assisted method. If 3 attempts at contrast-assisted cannulation of the pancreatic duct were unsuccessful, wire-guided cannulation (WGC) was attempted instead using a 0.035-inch guidewire (Jagwire, angle type; Boston Scientific, Boston, MA, USA). If cannulation by WGC was unsuccessful, precut was performed.

Study outcomes
The primary outcome of the study was the development of PEP, which was defined according to the criteria of Cotton et al. [1]. PEP was diagnosed if there was new onset of pain in the upper abdomen and elevation of serum amylase level to >3 times the upper limit of normal within 24 hours after ERCP, and prolonged hospitalization for ≥2 days. The severity of pancreatitis was graded as mild when hospitalization lasted 2 to 3 days, moderate for 4 to 10 days, and severe when prolonged for >10 days or any of the following occurred: hemorrhagic pancreatitis, pancreatic necrosis, pancreatic pseudocyst, or a need for percutaneous drainage or surgery. The secondary outcome was serum amylase level at 2 hours after ERCP as a predictor of PEP.

Sample size and statistical analysis
We planned a prospective, randomized, placebo-controlled trial. Prior data indicate that the PEP rate among controls is 0.18 [6, 17]. If the true PEP rate is 0.04 with reference to previous studies [6, 17], we would have needed 182 patients to be able to reject the null hypothesis that the PEP rates for experimental and control subjects were equal with probability (power) 0.8. Type I error probability associated with this test of the null hypothesis was 0.05. We used an Fisher’s exact test to evaluate this null hypothesis. Categorical variables were analyzed with χ² test, Fisher’s exact test and Mann–Whitney U-test, as appropriate, while continuous variables were analyzed using Student’s t test. Risk factors for PEP were examined by univariate and multivariate analyses and calculated with odds ratio (OR) with 95% confidence interval (CI), using a logistic regression method. Statistical significance was set at P<0.05. Statistical analysis was performed using the Excel-Toukei 2010 for Windows (Social Survey Research Information, Tokyo, Japan).

Results

Patients and discontinuation
From August 2013 to March 2015, a total of 144 patients were enrolled (Fig. 1). In March 2015, we performed an interim analysis that has not been preplanned at the first 100 patients and recommended early termination of the study on the basis of the benefit of flurbiprofen axetil as compared with placebo for ethical reasons. A total of 47 patients received flurbiprofen axetil, and 53 received placebo (Fig. 1). All patients completed follow-up to the primary and secondary endpoints. Baseline characteristics and indications for ERCP were similar in the 2 groups (Table 2 and Table 3).

Study outcomes
The primary outcome of PEP occurred in 11 of 100 patients (11%); 2 of 47 patients (4.3%) in the flurbiprofen group and 9 of 53 patients (17%) in the placebo group. The incidence of PEP was lower in the flurbiprofen group (P=0.041). In addition, all instances of PEP in the flurbiprofen group were mild. However, in the placebo group, PEP was mild in 6 patients and moderate in 3 (Fig. 2). Absolute risk reduction was 12.7% and the number needed to treat (NNT) was 7.9. Relative risk reduction (RRR) was 62.4. The secondary outcome, hyperamylasemia at 2 hours after ERCP, was observed in 22 of 100 patients (22%); 8 of 47 patients (17.0%) in the flurbiprofen group and 14 of 53 patients (26.4%) in the placebo group (P=0.109) (Fig. 2). No AEs related to flurbiprofen axetil were reported.

The relative benefit of flurbiprofen axetil differed according to PEP risk score. With a risk score of 1 or 1.5 points, PEP occurred in 1 of 36 (2.8%) patients and 7 of 42 (16.7%) patients, respectively.
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Discussion

This study showed that IV injection of low-dose flurbiprofen axetil immediately after ERCP reduced PEP in high-risk patients. In addition, it may reduce moderate and severe PEP. However, flurbiprofen axetil did not reduce hyperamylasemia at 2 hours after ERCP. In this study, the NNT to prevent PEP in high-risk patients was 7.9. This was similar to a previous study of rectal NSAIDs use [6], and the incidence of PEP in patients with 0 or 0.5 risk points indicated 1.9% (9/463) in our institution. Therefore, we considered that NSAID administration was unnecessary for low-risk patients. PEP risk score was decided after ERCP, we made a study design to low-dose flurbiprofen injection after ERCP. Furthermore, flurbiprofen axetil was considered easier to administer than rectal NSAIDs because of its intravenous route. This study revealed that IV injection of low-dose flurbiprofen axetil was an effective, safe and easy method for the prevention of PEP.

We administered nafamostat mesilate to the patients in both groups. Nafamostat mesilate has been reported to prevent PEP [15], so administration of a protease inhibitor is strongly recommended based on Japanese guidelines [25]. Therefore, it was difficult to design a study that would not include the administration of a protease inhibitor. The possibility exists that the effects of flurbiprofen axetil may be dependent on nafamostat mesilate. The possibility exists that the effects of flurbiprofen axetil may be dependent on nafamostat mesilate.

PEP are not fully understood although the mechanisms are believed to be multifactorial [4, 18]. One such factor is the patient’s inflammatory reaction to irritation of the pancreatic duct, in which ERCP plays a role [19-21]. NSAIDs are potent inhibitors of phospholipase A2, cyclooxygenase, and neutrophil-endothelial interactions, all of which are involved in inflammation of the pancreatic duct. Thus, it is believed that NSAID administration may be of benefit in preventing pancreatitis. Several meta-analyses and randomized controlled trials have revealed that rectal NSAIDs are effective [12-15, 22]. Most of those studies adopted a dose of 100 mg of rectal NSAIDs, which is not suitable for Asian patients. So, Otsuka et al. reported that 50 mg rectally diclofenac before ERCP was effective in Asian patients [17]. Although the efficacy of NSAIDs is reportedly dose-dependent [23], it is suggested that low-dose NSAIDs exert activity against PEP. However, NSAIDs were administered to all patients before ERCP in this study. Side effects are common with NSAIDs use [6], and the incidence of PEP in patients with 0 or 0.5 risk points indicated 1.9% (9/463) in our institution. Therefore, we considered that NSAID administration was unnecessary for low-risk patients. PEP risk score was decided after ERCP, we made a study design to low-dose flurbiprofen injection after ERCP. Furthermore, flurbiprofen axetil was considered easier to administer than rectal NSAIDs because of its intravenous route. This study revealed that IV injection of low-dose flurbiprofen axetil was an effective, safe and easy method for the prevention of PEP.

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Flurbiprofen axetil did not reduce hyperamylasemia at 2 hours after ERCP. Hyperamylasemia is useful in the diagnosis of PEP, and LaFerla et al. reported that amylase at 2 hours after ERCP was useful for the prediction of PEP. Hyperamylasemia is thought to be caused by injury of the pancreatic duct or pancreatic parenchyma associated with ERCP. In this study, the specificity of hyperamylasemia was 25% in the flurbiprofen group and 64.3% in the placebo group. The peak concentration of flurbiprofen axetil was reached 6.7 minutes after IV administration and the elimination half-time is 5.8 hours [26]. This suggests that, once flurbiprofen axetil is reached, the anti-inflammatory effect of flurbiprofen axetil is dose-dependent [23]. Therefore, PEP cannot be prevented by flurbiprofen axetil because the anti-inflammatory effect of flurbiprofen axetil effect is dose-dependent [23]. Therefore, PEP cannot be prevented by flurbiprofen axetil in the group with PEP risk scores ≥2 but severe pancreatitis can be prevented. In the future, we plan to conduct a comparative study of low-dose and high-dose flurbiprofen axetil in patients with a PEP risk score ≥2.

In this study, we attempted cannulation using a conventional catheter by contrast-injection cannulation methods. If this approach failed, we attempted WGC. WGC is the preferred technique because of its association with higher cannulation rates and lower risk of PEP, as reported by Cennamo V et al [27]. However, subsequent studies have reported conflicting results. Nambu et al. reported that the incidence of PEP tended to be lower with the WGC method than with contrast-injection methods, although the success rate of cannulation was comparable [28]. Kawakami et al. and Kobayashi et al. reported that the WGC technique did not reduce PEP and did not improve the success rate of selective bile duct cannulation over contrast-injection methods [29, 30]. Therefore, we cannot conclude that WGC is superior to contrast-injection methods in terms of effectiveness and safety. For that reason, initial attempts at cannulation in this study were made using the contrast-injection cannulation method, with which the researchers were more familiar.

There were 3 limitations of this study. First, the study was conducted at a single center. Second, pancreatic duct stent placement was left to the discretion of the endoscopist. In this study, a pancreatic duct stent was placed where a guidewire remained stuck, and severe PEP did not occur in the flurbiprofen group. However, a result might change if numbers increase because there were fewer patients with a PEP risk score ≥2. We hypothesize that the incidence of PEP in the group with PEP risk scores ≥2 was reduced by increasing the quantity of Flurbiprofen axetil because the anti-inflammatory effect of flurbiprofen axetil effect is dose-dependent [23]. Therefore, PEP cannot be prevented by flurbiprofen axetil in the group with PEP risk scores ≥2 but severe pancreatitis can be prevented. In the future, we plan to conduct a comparative study of low-dose and high-dose flurbiprofen axetil in patients with a PEP risk score ≥2.

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following ERCP. Pancreatic stents were not placed where good discharge of the contrast agent in the pancreatic duct was observed. However, multivariate analysis showed that placement of the pancreatic stent was not significantly affected by reduced PEP (Table 5). Third, interim analysis was not preplanned. As this was a single-blind study, we found that in the first 100 patients, administration of flurbiprofen reduced PEP, and an interim analysis showed its usefulness. Because PEP has been demonstrated to be a fatal complication, we stopped this prospective study. Further multicenter study will be required to determine the efficacy of flurbiprofen.

**Conclusion**

In conclusion, IV injection of low-dose flurbiprofen axetil in high-risk patients is an effective, safe and easy method in the prevention of PEP.

**Competing interests:** None

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