Original Article

Efficacy of Postprocedure Administration of Parecoxib Sodium in the Prevention of Post-ERCP Pancreatitis

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ABSTRACT

Objective: Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Many medications have been used to prevent this complication. The purpose of this study was to evaluate the efficacy of intravenous parecoxib sodium administered for the prevention of post-ERCP pancreatitis.

Methods: During 9 months, all eligible patients who underwent ERCP were enrolled in this study. Patients were randomly received an intravenous parecoxib sodium, 40 mg, immediately after ERCP or not. At the end of each procedure, age, sex, indication of ERCP, findings and the details of the maneuvers performed were recorded by endoscopists. Serum amylase levels and clinically pertinent evaluations were obtained in all patients after ERCP.

Results: A total of 60 patients entered the trial, of which half received parecoxib sodium. Eight patients developed pancreatitis; four cases in the parecoxib sodium group and four cases in the control group. The procedures characteristics and developing acute pancreatitis in each group did not show significant difference. Serum amylase level at 4 hours post ERCP and next day seem to be lower but not significant in parecoxib sodium group compared to those among control group.

Conclusions: Considering a relatively small sample size of the present study, intravenous administration of parecoxib sodium immediately after ERCP could not reduce the incidence and severity of post-ERCP pancreatitis.

Key words : parecoxib, acute pancreatitis, ERCP

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INTRODUCTION

Acute pancreatitis is the most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP). Post-ERCP pancreatitis occurs in 1-10% of patients but may approach 25% or more depending on the presence of risk factors. These included young age, female gender, difficulty in bile duct cannulation, pancreatic sphincterotomy, and sphincter of Oddi dysfunction.[1-3] Most cases of post-ERCP pancreatitis are mild or moderate pancreatitis but severe pancreatitis occurs in 0.4-0.6% of cases.[4,5] Several agents have been tested in clinical trials, but none is used routinely in clinical practice. The use of proteinase inhibitors such as gabexate mesylate in the prevention of post-ERCP pancreatitis has been disappointed.[6,7] Somatostatin is likely to be ef fective in the prevention of post-ERCP pancreatitis.[8,9] Cellular events leading to pancreatitis involve an inflammatory process with premature activation of trypsin in acinar cells.[10] Phospholipase A_2 is believed to play a critical role in the initial inflammatory cascade of acute pancreatitis by regulating a number of proinflammatory mediators, including arachidonic acid products and platelet-activating factors.[11] Prevention or interruption of this cascade may prevent development of pancreatitis and its consequences. It has been shown that nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of phospholipase A_2 activity in the serum of patients with severe acute pancreatitis.[12] NSAIDs have also been shown to have beneficial effects in experimental acute pancreatitis.[13] It had been shown that rectal diclofenac[14] and rectal indomethacin can reduce the incidence of post-ERCP pancreatitis.[15] Unfortunately, prophylactic orally administered diclofenac was not observed to affect the frequency or severity of post-ERCP pancreatitis in high-risk patients.[16]

Cyclooxygenase (COX) is the key enzyme in the synthesis of prostaglandins from arachiodonic acids. It has two isoforms. COX-1 is constitutively expressed in all types of the tissues and cells and produces prostaglandins for physiological reactions including the maintenance of mucosal integrity, normal secretion and motor functions and microcirculation. On the other hand, COX-2 is induced by proinflammatory cytokines generated in inflamed tissues and inflammatory cells.[17] It has been shown during the acute pancreatitis that COX-2 mRNA expression increases, while COX-1 expression remains constant.[18] Therefore, COX-2 inhibitors such as celecoxib and parecoxib were used for the treatment of the acute pancreatitis in the experimental animal studies, and the beneficial effects on the course of the acute pancreatitis were reported.[19-24]

Parecoxib is a prodrug of valdecoxib. It has been used as non-narcotic analgesic for severe post-surgical pain and has application in other acutely painful conditions. We conducted a prospective, single-center, randomized, controlled trial to determine whether a single dose intravenous parecoxib sodium given immediately after ERCP reduce the incidence of post-ERCP pancreatitis.

PATIENTS AND METHODS

This study was designed as a randomized, prospective, single-center trial, which was approved by the ethical committees. From May 2008 to January 2009, all consecutive patients with age more than 18 years old who underwent therapeutic ERCP were asked to give informed consent to participate in the study. ERCP procedures were performed by training endoscopists under the supervision of 5 experienced endoscopists (T.S., J.J., W.P., S.S. and S.C.). Exclusion criteria from the study were the following: patients who had taken NSAIDs during the preceding week, those who had developed acute pancreatitis during 2 weeks before the procedure, those with a history of chronic pancreatitis, renal failure ($Cr \geq 1.5$ mg/dl), known allergy to NSAIDs, aspirin, or COX-2, patients who had any contraindications to receiving parecoxib sodium [hypersensitivity to sulfonamide, bronchospasm, severe hepatic impairment (Child- Pugh score more than 9), post coronary artery bypass graft, severe congestive heart failure, active peptic ulcer, or gastrointestinal bleeding], pregnancy or lactation, previous sphincterotomy and refusal to participate.

ERCP was performed with a standard duodenoscope. Midazolam and meperidine were used during the procedure. Some cases needed hyoscin-N-butyl bromide. Lopamidol was used as contrast medium. Cannulation was performed with the guidewire method (i.e. the wire enters the duct before any injection) so that a very small amount of contrast was injected in the pancreatic duct. Prophylactic pancreatic stents to prevent post-ERCP pancreatitis were not placed in any subject.

Enrolled patients were randomized fashion with

concealed allocation. Patients received an intravenous parecoxib sodium, 40 mg, or not, immediately after ERCP. At the end of each procedure, the endoscopist recorded the age, sex, indication of ERCP, ERCP finding and the details of the maneuvers performed, particularly the ease or difficulty of cannulation, number of cannulations, number of pancreatic duct injections, presence, if any, of pancreatic acinar filling on radiography, number of times the guide wire entered the pancreas, sphincterotomy, precut sphincterotomy, stone extraction and stent placement. Trainee involvement in the procedure was allowed to have 15 minutes and not more than 3 attempts to cannulate.

Serum amylase levels were obtained at 4 hours after completion of ERCP procedures. If the 4-hour serum amylase level was less than 150 IU/L and there was no clinical evidence of acute pancreatitis, patients were allowed to receive free oral fluids and diet. If the 4-hour serum amylase level was more than 150 IU/L or patient exhibited epigastric pain with guarding, referred pain to back, or nausea and vomiting, patients were fasted and intravenous crystalloid fluids with appropriate analgesia were prescribed. In the next morning, patients were evaluated for clinical evidence of acute pancreatitis and serum amylase levels were measured. Prolongation of hospitalization and treatment modality for complications were discrete by managing physicians.

Definitions

Cannulation difficulty was defined base on the number of attempts on the papilla with a cannulating instrument.[16,26] Cannulation was defined as easy when 1 to 5 attempts took place, as moderate difficult when 6 to 15 attempts took place and as difficult when more than 15 attempts occurred.

According to the consensus definition,[25] post-ERCP acute pancreatitis was defined on the basis of a serum amylase more than 3 times the upper limit of normal for the reference laboratory (≥ 150 IU/L) in conjunction with epigastric pain, referred pain to back, and rebound tenderness occurring within 24 hours after ERCP. Those was graded as mild, moderate, severe: Mild = serum amylase at least three times normal at more than 24 hours after procedure requiring admission or prolongation of planned admission for 2-3 days; moderate = hospitalization for 4-10 days; severe = hospitalization for more than 10 days, or hemorrhagic pancreatitis, phlegmon or pseudocyst, or required intervention such as percutaneous drainage or surgery.

Statistical Analysis

Sample size was calculated with 80% power to detect a reduction of acute pancreatitis rate from 15.4% to 6.3 % at a significance level of 0.05.[14] The estimated number of patients needed was 185 for each group. Statistical analysis for categorical data was performed with the Pearson χ^2 test and the Fisher exact test when appropriate, whereas numeric data were analyzed with the Mann-Whitney U test, with $p < 0.05$ indicating a significant difference.

RESULTS

Between May 2008 and January 2009, a total of 60 patients fulfilled the entry criteria and accepted to participate. About half of patients received parecoxib sodium. There were 11 women in the parecoxib sodium group and 15 women in the control group. The patients were well matched in regarding to age (mean ± SE; parecoxib sodium, 64.7 ± 16.2 years; control group, 61.2 ± 16.4 years). Patients' characteristics and indications for ERCP were not significantly differed between both groups. (Table 1)

None of the procedures characteristics and the prevalence of acute pancreatitis in each group were significantly different. (Table 2) Four hours after the endoscopic procedure, the serum amylase level (mean ± SD) was 159 ± 383 IU/L in the control group and 81 ± 145 IU/L in the parecoxib sodium group. The morning after the endoscopic procedure, the mean serum amylase level was 185 ± 443 IU/L in the control group but only 112 ± 266 IU/L in the parecoxib sodium group. Serum amylase level at 4 hours post-ERCP and next morning was seem lower in parecoxib sodium group than control group but do not reach statistical significance. (Table 4)

Overall, eight patients developed acute pancreatitis; four cases were in the parecoxib sodium group and another four were in the control group. This preliminary data suggested no protective effect of parecoxib sodium. (Table 3) One patient in parecoxib sodium group developed severe post-ERCP pancreatitis. This patient was 69-year-old male presented with jaundice and had the diagnosis of cholangiocarcinoma. About procedure in this patient, common bile duct was easily cannulated, and the pancreatic duct was not can-

Table 1. Patients' characteristics and indications for ERCP.

	Parecoxib sodium (n = 30)	**Control (n = 30)**	***p*-value**
Age (yrs.)			0.420
mean ± SE	64.7 ± 16.2	61.2 ± 16.4	
median (range)	66.5 (19-83)	67.5 (23-88)	
Sex (M/F)	19 / 11	15 / 15	0.297
Indication for ERCP			0.395
• Choledocholithiasis	20 (66.7%)	16 (53.3%)	
• Jaundice	4 (13.3%)	7 (23.3%)	
• Cholangitis	4 (13.3%)	6 (20%)	
• Bile duct stenosis	2 (6.7 %)	0 (0 %)	
• Post-cholecystectomy bile leak	0 (0%)	1 (3.3%)	

Table 2. Procedure characteristics; all patient (n = 60) / patients with pancreatitis (n = 8).

	Parecoxib sodium (n = 30)	**Control (n = 30)**	***p*-value***
Success cholangiography	29/3	30/4	1.00/1.00
Difficult cannulation			0.336/1.00
• Mild (1- 5 attempts)	27/3	25/3	
• Moderate (6-15 attempts)	2/0	5/1	
• Severe (>15 attempts)	1/1	0/0	
Success pancreatography	10/3	3/1	0.053/0.486
Biliary sphincterotomy	25/2	24/2	0.739/1.00
Pancreatic duct cannulations			0.296/0.564
Mean ± SE	1.63 ± 1.41 / 2.33 ± 2.31	1 ± 0 / 1 ± 0	
Median (range)	0 (0-5)	0 (0-1)	
Lithotripters	1/0	3/0	0.612/-
Balloon extraction	17/1	16/1	0.795/1.00
Basket	0/0	1/0	1.00/-
CRE Dilatation**	5/0	3/0	0.706/-
Precut sphincterotomy	2/1	0/0	0.492/1.00
Biliary stent placement	6/1	10/3	0.243/0.486

**p* values for each study arm in all patients and in patients with pancreatitis
**CRE Dilatation = Controlled radial expansion dilatation

Table 3. Incidence of post ERCP pancreatitis.

	Parecoxib sodium (n = 30)	**Control (n = 30)**	***p* value**
Pancreatitis (%)	4 (13.3%)	4 (13.3%)	1.00
• Mild	3	4	
• Moderate	0	0	
• Severe	1	0	

Table 4. Serum amylase level of the patients.

Serum amylase (IU/L)	Parecoxib sodium (n = 30)		Control (n = 30)		*p* value
	(Mean ± SD)	Median (range)	(Mean ± SD)	Median (range)	
4th hr after ERCP	81 ± 145	29.5 (5 - 561)	159 ± 383	27 (10 - 1835)	0.988
Next morning after ERCP	112 ± 266	28 (2 - 1101)	185 ± 443	25 (10 - 1945)	0.700

nulated or injected. Precut sphincterotomy was done and two plastic stent was inserted to left and right intrahepatic bile ducts. He died at 4th day after procedure due to severe sepsis.

DISCUSSION

ERCP providing a unique opportunity to administer a prophylactic medication at the time of the pancreatic insult is well defined. An ideal prophylactic pharmacological agent must fulfill the following prerequisite criteria: the entity that needs prevention must occur frequently, cause significant morbidity and/or mortality that warrants its avoidance, the agent must be easily administered, demonstrating clinical efficacy, preferably be low cost, and being free from hazardous side effects.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and indomethacin have been investigated in a number of trials, with slightly encouraging, but results were still conflicted. Elmunzer et al conducted a well-designed meta-analysis, which was able to recognize statistical homogeneity in the studies evaluated, permitting a reliable conclusion despite methodological differences, mainly in design.[27] The authors selected for their meta-analysis only four trials evaluating a rectally administered drug, so they excluded the study by Cheon et al because they used the oral route for diclofenac. They recognized a similar risk for post-ERCP pancreatitis among all four series, and concluded that the efficacy of prophylactic NSAIDs with diclofenac or indomethacin, which were applied to both standard- and high-risk patients, had a similar relative risk reduction. It was important to note that high-risk cases enjoy the greatest benefit. The meta-analysis showed the efficacy of a single rectal dose of NSAIDs administrated immediately before or after the ERCP had tendency toward in reducing the frequency and severity of post procedure pancreatitis. It was noticed that only two NSAIDs were used. There were in two studies involving use of indomethacin and other two used diclofenac for treatment. Whether there was a difference in prophylactic effect between the two drugs and whether other NSAIDs possess the same effect needs further investigation.

We conducted a randomized trial to demonstrate efficacy of intravenous parecoxib sodium given immediately after ERCP procedure for preventing post-ERCP pancreatitis in human. The results seem to show that parecoxib sodium can not prevent post-ERCP pancreatitis, however this may be in part due to relatively small sample size for demonstrating any protective effect of this agent. Considering the low incidence of post-ERCP pancreatitis (overall mean rate, 5%; low-risk cases, 2%), large numbers of patients are warranted to demonstrate if any significant results. Actually, the current study requires a total of 906 participants enrollment into the study to evaluate the efficacy of parecoxib to reduce an estimated standard post-ERCP pancreatitis rate by 50%. Therefore, studies should only be designed on a multicenter basis or be carried out over a number of years in a single center to ensure convincing results. This study demonstrated that there was no relationship between patient characteristics, maneuvers perform, and the risk factor to develop post-ERCP pancreatitis. In fact, up to now, there was no routine prophylaxis adopted in the majority of centers that conduct ERCP procedures. This might reflects that most endoscopists believe that expertise and technique, more than pharmacologic prophylaxis, play a major role in the prevention of post procedure pancreatitis. In non-risk subjects, who had a mean pancreatitis rate of 2%, pharmacologic prevention was not required; but in high-risk patients, who had a mean risk of post procedure pancreatitis of 10% or more, the search for effective prophylaxis is still justified. The

post-ERCP pancreatitis in this setting seems to be unrelated to the operator's experience and endoscopic technique, and is only partly prevented by pancreatic stenting, which may not be feasible in all cases.

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