

Efficacy of chymotrypsin in the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis

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Background

Pancreatitis is common after endoscopic retrograde cholangiopancreatography (ERCP).

Aim

To assess the pharmacological effect of diclofenac, allopurinol and chymotrypsin in the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis (PEP).

Settings and design

Calcular obstructive jaundice patients without pancreatitis scheduled for ERCP were randomized into three groups.

Materials and methods

The diclofenac group received 200 mg rectal suppositories immediately after ERCP, allopurinol received oral 300 mg 3h before ERCP, and chymotrypsin received intramuscular injection immediately after ERCP. Serum amylase and lipase were measured before, 1, 6, and 24 h after ERCP and procedure-related risk factors for post-ERCP pancreatitis were recorded. Pancreatitis was considered when serum amylase or lipase levels elevated more than three times the upper limit of normal with newly developed abdominal pain lasting at least 24 h after ERCP.

Statistical analysis

Analysis of variance for continuous variables and χ^2 for categorical variables.

Results

One hundred and fifty patients were included; diclofenac group (58 patients, 29 men, mean age 46.9±13.2 years), allopurinol (38 patients, 20 men, mean age 43.1±14.7 years) and chymotrypsin (54 patients, 28 men, mean age 40.6±17.3 years). Twelve (8%) patients developed PEP: the diclofenac group ($n=4$; 6.9%), allopurinol ($n=6$; 15.8%) while chymotrypsin ($n=2$; 3.7%), but this was not statistically significant ($P=0.318$). In patients who received chymotrypsin, regression of serum amylase and lipase to normal levels was much better compared with the other groups and was associated with better clinical improvement.

Conclusion

Chymotrypsin and allopurinol are comparable to diclofenac in the prevention of pancreatitis post-ERCP. Beside its prophylactic role, chymotrypsin could be effective in rapid improvement if PEP occurs.

Keywords:

chymotrypsin, endoscopic retrograde cholangiopancreatography, pancreatitis

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Introduction

Pancreatitis is common after endoscopic retrograde cholangiopancreatography (ERCP) (3.5–15%); fortunately in 90% of cases it is of mild or moderate degree, but if severe it could be associated with high morbidity and mortality [1,2]. Postendoscopic retrograde cholangiopancreatography pancreatitis (PEP) is defined as clinical pancreatitis with amylase or lipase at least three times the upper limit of normal at more than 24 h after the procedure, which requires hospital admission or a prolongation of planned admission [3]. The proteolytic enzyme chymotrypsin is known for its potent anti-inflammatory properties [4,5].

The aim of this study was to compare the effectiveness of diclofenac, allopurinol, and chymotrypsin in the prevention of PEP.

Patients and methods

This prospective, randomized, controlled study included consecutive adult patients who were presented to the endoscopy unit for ERCP due to

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calcular biliary obstruction. Written informed consent was obtained from all eligible patients prior to enrolment into the study. The study was approved by the local ethics committee.

The exclusion criteria included: (a) pregnancy or lactation, (b) malignancy, (c) patients with renal or liver disease, (d) contraindications to diclofenac, (e) allergy to allopurinol use or chymotrypsin, and (f) preprocedure acute pancreatitis evidenced by clinical examination and biochemical markers.

Eligible patients were randomized to receive either rectal diclofenac sodium 200 mg immediately after ERCP; chymotrypsin 5 mg, intramuscular, immediately after ERCP (skin sensitivity test was made before injection); or oral allopurinol 300 mg 3 h before the procedure.

A single operator performed all the procedures and was blinded to the prophylactic medication. Patients were kept NPO for at least 6 h after the procedure and were observed for at least 24 h afterward for signs of complications. Blood samples were obtained before and 1, 6, and 24 h after ERCP. Serum amylase and lipase activity were measured, normal ranges 0–100 and 0–190 IU/l, respectively.

All groups were matched as regards the procedure-related factors, indication for ERCP, and the amount of fluid administered in the perioperative period. Patients who had pancreatic duct injection were excluded to avoid its risk in developing PEP.

Diagnosis of post-ERCP pancreatitis was based on the presence of two of the three following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase more than three times the upper limit of normal, and/or (iii) characteristic findings from abdominal imaging. Severity of acute pancreatitis was assessed using Ranson's criteria [6].

Statistical methods

Data were analyzed using IBM SPSS statistics for Macintosh, version 22.0 (IBM Corp., Armonk, New York, USA). Continuous variables were compared among the three groups using the analysis of variance test followed by Tukey's test for intergroup comparisons. Categorical variables were compared among the three groups using χ^2 -test. Two-sided *P* was used in all analyses and was considered significant if less than 0.05.

Results

One hundred and fifty patients with calcular obstructive jaundice without pancreatitis scheduled

for ERCP were enrolled in our study. They were randomized to receive one of the prophylactic medications. Diclofenac group had 58 patients, 29 men, mean age was 46.9 ± 13.2 years; allopurinol group had 38 patients, 20 men, mean age was 43.1 ± 14.7 years, while the chymotrypsin group had 54 patients, 28 men, mean age was 40.6 ± 17.3 years. No adverse effects from the use of the three drugs was reported. The patients were comparable regarding age, sex, and baseline total and direct bilirubin, alanine transaminase, lipase, and prothrombin activity (Table 1).

Acute PEP was diagnosed in a total of 12 patients. Its incidence was comparable among the studied groups: four (6.9%) patients with diclofenac, two (3.7%) patients with chymotrypsin, and six (15.8%) patients with allopurinol. Although the chymotrypsin group has the lowest number of PEP, its prophylactic effect was not significant compared with the other two groups ($P=0.318$; Table 2). The procedures factors like sphincterotomy, requirement of precut and injection of the biliary duct showed no significant statistical differences in the development of PEP.

All patients who developed PEP were subjected to our standard treatment care which included good hydration with maintaining electrolyte balance and nutritional support. All of our patients developed mild to moderate pancreatitis and no patient

Table 1 Demographic and baseline biochemical characteristics of the studied groups

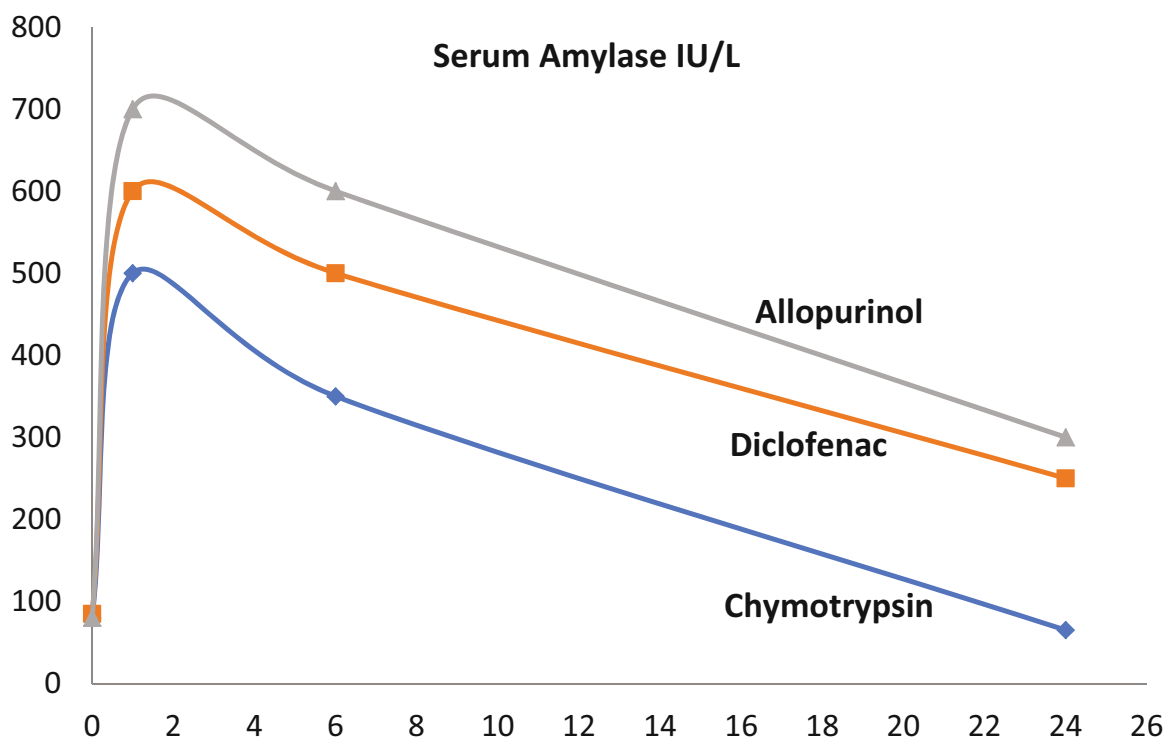
	Diclofenac (<i>n</i> =58)	Chymotrypsin (<i>n</i> =54)	Allopurinol (<i>n</i> =38)
Age (years)	46.9±13.2	40.6±17.3	43.1±14.7
Sex (male : female)	29 : 29	28 : 26	20 : 18
Total bilirubin (mg/dl)	8.7±6.2	11.3±6.8	9.9±6.1
Direct bilirubin (mg/dl)	6.2±4.3	8±5.7	7±4.6
Alanine aminotransferase (IU/l)	52.6±47.1	70.7±31.6	61.4±37.3
Aspartate aminotransferase (IU/l)	57.4±44.9	78.7±27.4	64.6±36.3
International normalized ratio	0.9±0.1	0.9±0.1	0.9±0.1

Table 2 Incidence of postendoscopic retrograde cholangiopancreatography pancreatitis

Post-ERCP pancreatitis	Diclofenac (<i>n</i> =58)	Chymotrypsin (<i>n</i> =54)	Allopurinol (<i>n</i> =38)	<i>P</i>
Yes (<i>n</i> =12)	4 (6.9)	2 (3.7)	6 (15.8)	0.318
No (<i>n</i> =138)	54 (93.1)	52 (96.3)	32 (84.2)	–

ERCP, endoscopic retrograde cholangiopancreatography.

Figure 1



Follow-up of mean serum amylase levels between the three groups after endoscopic retrograde cholangiopancreatography.

developed severe pancreatitis. All patients responded to the supportive treatment with no serious complications or mortality. The rate of amylase and lipase decline, which was associated with clinical improvement, was more rapid in the chymotrypsin group compared with the other two groups. Figures 1 and 2 represent and compare the progression of the mean values of amylase and lipase, respectively, between the three groups of PEP patients.

Discussion

Pancreatitis is a common complication after ERCP and sometimes could be life threatening. Understanding the injury mechanisms could help the researchers to pharmacologically prevent the cascade of events and subsequently reducing the risk of this complication. Unfortunately, because the exact mechanisms are unknown, studies using nifedipine [7], calcitonin [8], corticosteroid, somatostatin, and gabexate failed to show benefits in the prevention of PEP [3].

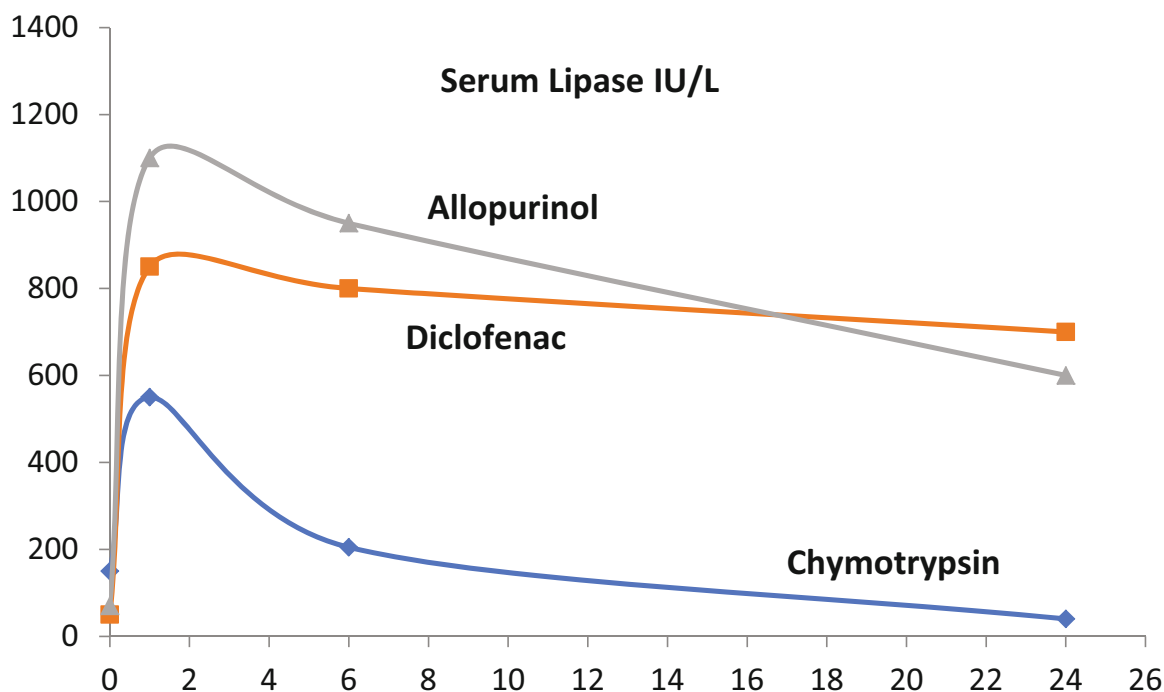
The NSAID, diclofenac, as a prophylactic drug is widely accepted in the prevention of PEP, owing to its potent inflammatory suppression [3]. Yet, studies over other drugs showed promising results like allopurinol, the xanthine oxidase inhibitor, which decrease the generation of oxygen-derived free radicals [9]. Also, chymotrypsin, the proteolytic enzyme exerts potent

anti-inflammatory and antiedematous properties leading to resolving of inflammation and facilitates the repair process [4]. In this study, we tried to test the efficacy of these three well-known medications in the prevention of PEP. Our results showed that no statistical difference in the incidence of acute pancreatitis among the studied groups was noticed, although the number of PEP was much less with the chymotrypsin group ($n=2$; 3.7%), then the diclofenac group ($n=4$; 6.9%), and lastly the allopurinol group ($n=6$; 15.8%). This could mean that although diclofenac is the standard of care, we can use chymotrypsin in patients who cannot tolerate it.

Additionally, our results showed that in patients who developed PEP, their decline rate of amylase and lipase beside the associated clinical improvement was more rapid in the chymotrypsin group compared with the two other groups. We think this potential therapeutic effect of chymotrypsin needs further work on a larger group of patients to prove it. To our knowledge, this is the first study that evaluated the efficacy of chymotrypsin in preventing PEP.

Important concern about chymotrypsin safety is that as it is a foreign protein injected IM it could rarely induce allergic reactions. This necessitates a skin sensitivity test before injection, otherwise severe reactions could happen. However, it is a safe, cheap, and widely used

Figure 2



Follow-up of mean serum lipase levels between the three groups after endoscopic retrograde cholangiopancreatography.

medicine and is commonly used after surgical operations to prevent and treat postsurgical edema.

This study has the limitation of exclusion of any ERCP indication other than choledocholithiasis. We think that choledocholithiasis is the most common indication for ERCP, besides our plan was to have comparable patient and procedure factors between the three groups, so our results could reflect only the prophylactic effect of each medicine in its group.

Conclusion

The use of chymotrypsin seems superior to the standard of care use of diclofenac in prophylaxis of PEP and this could be of help in patients contraindicated to receive diclofenac. Furthermore, chymotrypsin potential value as a therapeutic drug of pancreatitis with acceleration of the biochemical and clinical improvement could justify its use over diclofenac in the prophylaxis of PEP; however, larger numbers of patients are required in the upcoming studies to demonstrate its effect.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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