Does Allopurinol Prevent Post Endoscopic Retrograde Cholangio-Pancreatography Pancreatitis? A Randomized Double Blind Trial

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Abstract- Post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is a frequent complication either for diagnosis or treatment of pancreatobiliary diseases. A number of pharmacological agents have been tried for prevention or alleviation of the complication. Allopurinol with free radical scavenger property has been considered as an effective prophylactic agent in some clinical trials. Administration of allopurinol in these trials was done in a long period before doing ERCP. Hence allopurinol converts to oxupurinol in the liver rapidly; it seems that clinical judgment about the net effect of allopurinol on prevention of post ERCP pancreatitis is doubtful. In this randomized double blind clinical trial, effect of allopurinol on prevention or alleviation of clinical and laboratory signs of pancreatitis has been evaluated in 74 patients undergoing ERCP. Results showed that there is not any difference between allopurinol and placebo in occurrence and severity of post ERCP pancreatitis (P=0.97). Also there is not any significant difference in amylase rises between 2 groups in 8 and 16 hours after ERCP (P=0.947, 0.287 respectively). Beneficial effects of allopurinol in some of the previous studies may be attributed to its active metabolite (oxypurinol). Further studies recommended about the net effect of allopurinol and oxypurinol in the complication.

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Keywords: Allopurinol; Cholangiopancreatography, endoscopic retrograde; Pancreatitis; Amylases; Oxypurinol

Introduction

Acute pancreatitis is the most frequent complication of endoscopic retrograde cholangio pancreatography (ERCP). Incidence of the problem was reported from %4 in low risk patients up to %40 in high risk patients (1,2). The exact mechanism of post ERCP pancreatitis is unclear, although a number of factors have been implicated as major potential causes of pancreatic injury. Several pharmacologic agents have been used for prevention or alleviation of post ERCP pancreatitis. Pancreatic secretion suppressants like octerotide (3), anti inflammatory agents like indomethacin (4) anti oxidants like beta carotene (5), protease antagonists such as gabexate (6), oddi sphincter relaxants such as nitrates (7) are the main categories that have been evaluated for prevention of pancreatitis after ERCP. Free radical scavenger property of allopurinol and oxypurinol (active metabolite of allopurinol) has been reported in the literature (8,9). As free radicals may be a cause of post ERCP pancreatitis, allopurinol may be effective in prevention or alleviation of the complication. Studies in animal model have demonstrated that pretreatment with allopurinol decreases the degree of pancreatic inflammation and serum hyperamylasemia in cases of ischemic-, alcohol-, gallstone, and pancreatography-induced pancreatitis (10,11). Some clinical studies have evaluated effect of allopurinol in alleviation or prevention of post ERCP pancreatitis. Two prospective studies in humans with allopurinol have yielded negative results with respect to prevention of post ERCP pancreatitis (12,13). However in another study allopurinol could result in alleviation of the complication significantly (14). In mentioned studies allopurinol has been administered more than 16 hours before ERCP and at this time, there is mainly oxypurinol

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(active metabolite of allopurinol) rather than allopurinol in the blood (15). In this study, the aim was to determine the net effect of prophylactic orally administered 2 doses of allopurinol on the frequency and severity of post ERCP pancreatitis.

Patients and Methods

Between February 2009 and July 2009, all patients undergoing ERCP in the gastrointestinal and liver diseases ward of Talighani Hospital, Tehran-Iran, enrolled the study. This ward is one of the well- known ERCP centers of Iran.

Exclusion criteria's were: 1) any type of renal failure, 2) any type of anemia, 2) acute pancreatitis during 2 weeks before ERCP, 3) age lower than 20, 4) pregnancy, 5) patients under treatment with azathioprin, 6) refusal or inability to give informed consent. The study was accepted by research center for gastrointestinal and liver diseases (RCGLD) and Ethics committee of Shahid Beheshti University of Medical Sciences according to declaration of Helsinki.

In a double-blind randomized clinical trial, patients were divided in 2 group, in group 1 patients received 2 separated doses of 300 mg allopurinol tablets, in group 2 patients received 2 separated doses of placebo tablets.

Dosage regimen was: 3 hours before doing ERCP and the other one just before doing ERCP. All patients had fasted over night before doing ERCP. The procedures were done under local anesthesia with lidocaine 2%. Also a combination of hyoscine, midazolam and meperidine were administered as premedication and during procedure.

The definition of post ERCP pancreatitis in present study was based on a consensus criteria; mild: amylase concentration at least 3 times above upper limit of normal at more than 24 hours after procedure requiring admission for 2-3 days, moderate: admission for 4-10 days and severe: admission for more than 10 days (16). For this purpose all the studied patients stayed in the hospital for at least 24 hours after ERCP and were observed clinically for evaluation signs and symptoms of acute pancreatitis.

Also before doing ERCP a blood sample was kept from the patient as base line. Then patients were undergone of ERCP. At the end of the procedure, 2 separated blood samples were kept from the patients (in 8 and 16 hours after ERCP procedure respectively). After finishing patient selection, the amylase concentrations of the samples were determined by using automated analyzer (Kodak Ektachem 700-XR analyzer C series, normal range 0-120 IU/L).

We use SPSS 15 for statistical analysis. Chi-square, Fisher exact and Man-Whitney test were used for comparison of 2 groups. P value< 0.05 was considered significant.

Results

During the study period 100 patients were selected. In some patients there are some problems leads to not complete the study finally. Arrhythmias, respiratory distress, falling oxygen saturation were the main causes of exclusion of selected patients. Finally 74 patients completed the study (29 in group 1 and 45 in group 2). Table 1 shows demographic data of patients. With regarding to sex, age and causes of ERCP doing there is not any difference between 2 groups (P= 0.609, 0.101, 0.074 respectively). Regarding to laboratory criteria, serum amylase concentration were determined at baseline (first time), 8 hours (second time) and 16 hours (third time) after doing ERCP. Table 2 shows the mean concentration of amylases in 3 different times. There is not any difference in the mean amylase concentration between group 1 and group 2 at first, second and third time (P=0.731, 0.947, 0.287 respectively).

Table 1. Demographic data of studied patients

Parameter		Allopurinol (n=29)	Placebo (n=45)	*P* value
Age	20-60	14	19	0.609
	>60	15	26	
sex	Female	21	24	0.101
	Male	8	21	
Causes of ERCP	Common Bile Duct stone	9	8	
	Cholangitis	6	9	0.074
	Cholangiocarcinoma	10	10	
	Pancreas mass	4	9	
	others	0	9	

Table 2. Mean±SD amylase concentration in 2 groups at different times of study

Amylase concentration(IU/mL)	Allopurinol (n= 29)	Placebo (n= 45)	*P*
Baseline amylase concentration (A0)	148.06 ± 42.62	107.04 ± 14.77	0.731
Amylase concentration 8 hours after ERCP (A1)	367.19 ± 128.29	410.95 ± 166.58	0.947
Amylase concentration 16 hours after ERCP (A2)	193.85 ± 45.92	405.34 ± 134.15	0.287

As both clinical and laboratory parameters are important for diagnosis of acute pancreatitis, we determined patients who have a new onset or elevated abdominal pain prolonged for more than 24 hours, resulted to admission of outpatient for more than 1 night and is accompanied with an increase in amylase concentration at least 3 times above upper limit normal. In this view, a total of 8 patients experienced abdominal pain requiring more than 1 night hospitalization with an amylase level 3 times upper limit of normal at 16 hours. Of them 3 patients were from alopurinol group (n=29) and 5 patients were from placebo group (n=45). Table 3 shows occurrence and severity of pancreatitis in studied patients. Analysis of Chi-square test showed that there is not any significant difference between 2 groups in the occurrence rate of pancreatitis or its severity regarding to clinical criteria (P=0.97)

Discussion

The mechanism(s) of post ERCP pancreatitis has not been known well. Oxygen derived free radicals may disrupt integrity of epithelial cells leading to capillary permeability and induction of pancreatitis (10). As allopurinol and oxypurinol (active metabolite) are specific inhibitors of xanthine oxidase, it is expected to inhibition or alleviation of early events in the cascade leading to post ERCP pancreatitis by these agents.

Allopurinol is an agent that has been used for treatment of huperurecemia for decades (16). Also it is not expensive and it's a safe compound. These characteristics make it a rational choice for prevention of pancreatitis in patients undergoing ERCP.

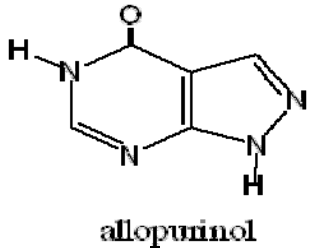
In order to evaluation the effect of allopurinol in prevention of pancreatitis after ERCP, Budzynska *et al*. compared effect of prednisone (40 mg), allopurinol (200 mg) or placebo 15 hours and 3 hours before doing ERCP. They reported that there is not any difference among the three regarding prevention of the post ERCP pancreatitis (12). In otherwise Katsinelos *et al.* evaluated effect of 600 mg allopurinol or placebo at 15 and 3 hours before ERCP on prevention or alleviation of pancreatitis. Opposite the result of previous study, they reported that the frequency of acute pancreatitis was significantly lower in the allopurinol versus the placebo group (P<0.001) (14). The different results of the two studies may be justified by increasing allopurinol dosage in the latter study.

Recently in a clinical trial in the Mexico, Martinez-Toreres *et al*. compared allopurinol (300 mg) versus placebo at 15 and 3 hours before the procedure. They reported that hyperamylasemia was more common in the placebo group (P=0.003) (17). This result states that allopurinol 300 mg may be enough to prevention of post ERCP pancreatitis.

In this study its preferred to match the patients as much as possible. Females and young age are two risk factors related to post ERCP pancreatitis (18). Our results show that there is not any difference between allopurinol and placebo groups regarding these risk factors.

Table 3. Occurrence and severity of pancreatitis in observed patients

	Total (n = 74)	Allopurinol (n = 29)	Placebo (n = 45)	*P*
No pancreatitis	66	26	40	
Mild pancreatitis	5	2	3	0.97
Moderate pancreatitis	3	1	2	
Severe pancreatitis	0	0	0	



allopurinol

Figure 1. Chemical structure of allopurinol

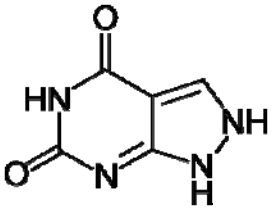


Figure 2. Chemical structure of oxypurinol

It's noticeable that although structure of allopurinol (Figure 1) and its active metabolite; oxypurinol (Figure 2) are similar, there is a difference in half lives of them. Half life of allopurinol in plasma is 1-2 hours however half life of oxypurinol is about 15 hours (15). It seems that in previous studies, because of the administration of allopurinol at 15 hours and 3 hours before the ERCP, both allopurinol and oxypurinol were in the plasma at time of doing ERCP. As both allopurinol and oxypurinol have antioxidant properties, it seems that some of the preventive effect on amylase raises related to oxypurinol instead of allopurinol.

In this study, the aim is evaluation the net effect of allopurinol on prevention of pancreatitis after ERCP. So administration of allopurinol was done at 3 hours and just before the ERCP. At this time with regarding to peak plasma of allopurinol and oxypurinol, there is a little concentration of oxypurinol in the plasma probably however there is a significant concentration of allopurinol. The results show that there was not any difference between allopurinol and placebo group. With regarding to previous studies, it means that may be oxypurinol is more important for prevention of pancreatitis after ERCP than allopurinol. In future, studies about the net effect of oxyurinol on prevention or alleviation of post ERCP pancreatitis are recommended.

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