Diclofenac versus Allopurinol for the prevention of post-ERCP pancreatitis: a prospective randomized controlled trial

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Abstract: Background: Pancreatitis is the most common complication following endoscopic retrograde cholangiopancreatography (ERCP), which can on occasions be severe and life threatening. **Aim:** To compare the efficacy of diclofenac, allopurinol 300 mg and allopurinol 600 mg for the prevention of post-ERCP acute pancreatitis. **Patients and Methods:** 130 patients were scheduled for ERCP either for diagnosis and or treatment of obstructive jaundice. Patients were randomized to receive a single dose of either: 100 mg diclofenac suppository immediately after ERCP (40 patients, 25 males, mean age 51.8±14.6 years), 300 mg oral allopurinol one hour before ERCP (30 patients, 16 males, mean age 53.3±11.5 years), 600 mg oral allopurinol one hour before ERCP (40 patients, 24 males, mean age 47.6±14.3 years) or no prophylaxis (control group) (20 patients, 14 males, mean age 46.9± 14.4 years). Serum amylase and lipase were measured immediately before, 4 and 24 hours after ERCP. Pancreatitis was considered when there was abdominal pain consistent with pancreatitis, coupled with the need for unplanned hospital stay or extension of the planned hospital stay by at least 2 days, with rise of serum amylase at least 3 times the upper normal level. **Results**: None of patients on diclofenac or large dose allopurinol developed post-ERCP pancreatitis, versus one patient on allopurinol 300 mg and two in the control group. Serum amylase and lipase increased significantly after ERCP in the diclofenac, allopurinol 300 mg and the control groups ($p<0.05$). In the allopurinol 600 mg group, serum amylase increased significantly at 4 hours after ERCP while serum amylase at 24 hours and serum lipase at 4 and 24 hours did not. **Conclusions:** high dose allopurinol (600mg) prevented the increase in serum amylase at 24 hours and serum lipase at 4, and 24 hours after ERCP. Both diclofenac and allopurinol 600 mg were associated with low incidence of post–ERCP pancreatitis. [Report and Opinion 2010;2(4):41-51]. (ISSN:1553-9873).

Key words: pancreatitis, ERCP, Lipase, Amylase, Allopurinol, diclofenac

1. Introduction:

Pancreatitis is the most serious adverse event complicating diagnostic and therapeutic ERCP. Elevation of pancreatic enzymes occurs in up to 30% of patients. On occasions, this may be associated with acute pancreatitis, which is associated with substantial morbidity and occasional mortality (Gottlieb and Sherman, 1998; Poon et al., 1999; Binmoelle et. al, 1992: Weiner et al.,1995; Cavallini et al., 1996; Barkin et al., 1991; Sherman et al., 1991; Panagiotis et al., 2005).

Cellular events leading to pancreatitis involve an inflammatory process with premature activation of trypsin in acinar cells (Whitcomb, 2003). Phospholipase A2 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 (Gross et al., 2003). Prevention or interruption of this cascade may prevent development of pancreatitis and its consequences. Although drug development has been impressive, the availability of effective drugs in the prevention and management of pancreatitis remains limited. There have been many attempts to minimize the incidence and the severity of post-ERCP pancreatitis (Tittobello, 1997; Hogan and Stenting, 1998; Makela et al., 1997).

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to have beneficial effects in experimental acute pancreatitis (Wildenhain etv al., 1998: Murray et al., 2003). Rectal diclofenac might provide a simple, cheap alternative, but large-scale studies are again needed (Moreto et al., 2003). Although initial studies show a benefit with prophylactic administration of nitrates (Freeman and Guda, 2004) or NSAIDs (Moreto et al., 2003), neither of these therapies could be generally recommended (Broe and Cameron, 1982).

A number of studies have demonstrated that an early step in the pathogenesis of acute pancreatitis is

capillary endothelial injury manifested by an increase in capillary permeability (Sanfey and Cameron, 1984; Sanfey et al., 1984). These findings have prompted attempts at prevention of pancreatitis by treatment with free-radical scavengers (superoxide dismutase, dimethyl sulfoxide, and catalase), protease inhibitors (gabexate), and xanthine oxidase inhibition (allopurinol) (Sanfey et al., 1983; Cavallini et al., 1996; Masci et al., 2003; Sanfeyet al.,1985; Nordback and Cameron, 1993). Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine, which generates an oxygen-derived free radical. This catalyst is commonly derived from inactive precursor, xanthine dehydrogenase, which is present in the pancreas and the intestinal mucosa. Xanthine dehydrogenase is converted to xanthine oxidase by the proteolytic cleavage of a peptide fragment (Sanfey et al., 1983; Cavallini et al., 1996).

Allopurinol, an inhibitor of oxygen-derived free radical production, is a structural analog of the natural purine base hypoxanthine, an inhibitor of xanthine oxidase. Allopurinol is approximately 90% absorbed in the GI tract. Peak plasma levels for allopurinol and its metabolite, oxipurinol, generally occur at 1.5 hours and 4.5 hours, respectively, after oral ingestion. Oxipurinol, however, has a longer plasma half-life (approximately 15 hours), and, therefore, effective xanthine oxidase inhibition is maintained over a 24-hour period with a single dose of allopurinol. The efficacy of oral allopurinol to reduce post-ERCP pancreatitis was investigated in an in vivo animal model (Clemens et al., 1991). This supported the need for human studies on the utility of allopurinol pre-treatment to reduce the incidence of ERCP-induced pancreatitis. So far, two small trials which reported no beneficial effect have been published (Budzynska et al., 2001; Cotton et al., 1991).

The aim of the present study was to investigate three prophylactic regimens in the prevention of ERCP induced pancreatitis: oral high-dose (600mg) allopurinol compared to low dose (300mg) allopurinol compared to a single rectal suppository of 100 mg diclofenac in a prospective randomized trial.

2. Patients and methods

This study included 130 patients (mean age 49.7 ± 16. 7 years, 79 males and 51 females) with obstructive jaundice undergoing ERCP at the National Liver Institute, Minufiya University, Egypt. Exclusion criteria included; (1) Active acute pancreatitis as evidenced by clinical and biochemical evaluation, (2) Contraindications to diclofenac such as peptic ulcer, gastritis, bronchial asthma, liver cirrhosis, or allergy to diclofenac (3) Allergy to or current allopurinol use, and (4) pregnancy or lactation.

Patients were randomized into four groups: group 1; 40 patients (mean age 51.8± 14.6 years, 25 males) who received 100 mg rectal suppository of diclofenac just immediately after ERCP, group 2; 30 patients (mean age 53.3± 11.5 years, 16 males) who received 300 mg oral allopurinol one hour before ERCP, group 3; 40 patients (mean age 47.6 ± 14.3years, 24 males) who received 600 mg oral allopurinol one hour before ERCP and group 4; 20 patients (mean age 46.9 ± 14.4years, 14 males) who received no prophylaxis. All study groups were subjected to thorough history taking, clinical examination, biochemical tests including; alkaline phosphatase, γ-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, prothrombin time and concentration, total and direct bilirubin, serum albumin, serum creatinine, complete blood counts and abdominal ultrasonography.

Before ERCP, all patients were fasted overnight; sedation was provided using meperidine and midazolam. All procedures were performed by two experienced endoscopist using Fujinon ED450XT and Fujinon ED400XL doudenoscopes.

At the end of each procedure, the researchers recorded the details of the manoeuvres performed, including the total time length of the procedure, the number of cannulation attempts, the number of pancreatic duct cannulations, pancreatic acinarization on radiography, the existence of juxta-ampullary diverticulum, the final diagnosis, and whether a sphincterotomy or needle knife pre cut were done. Common bile duct (CBD) cannulation was rated by the endoscopist as ‘‘easy’’ or’ difficult’’ (requiring three or more attempts to achieve selective cannulation of the CBD).

The patients continued fasting for 6 hours after the end of the procedure. Serum amylase (normal: 0-100 U/L) and lipase (normal: 0-190 U/L) were estimated just before, 4 and 24 hours post procedure. They were performed using commercial kits (Randox company, Germany). If the 4-hours serum amylase level or serum lipase was less than 3 times the upper normal limit and there was no clinical evidence of acute pancreatitis at that time, free oral fluids and diet were allowed after 6 hours from the end of procedure. If the 4 hours serum amylase or serum lipase level was more than 3 times the upper normal limit and the

patient exhibited pain or nausea and vomiting, the patient was kept fasting, intravenous crystalloid fluids and opiate analgesics were prescribed. Patients with persistent signs and symptoms of pancreatitis after 48 hours underwent contrast-enhanced computed tomography (Odes et al., 1977).

Post-ERCP acute pancreatitis was considered with the occurrence of abdominal pain, tenderness, nausea and/or vomiting lasting more than 6 hours with serum amylase and/or lipase increasing above 3 times the upper limit of normal and was graded as mild, moderate, or severe based upon a consensus definition (33) Considered mild: serum amylase at least three times the high normal value persistent more than 24 hours after the procedure requiring admission or prolongation of planned admission for 2–3 days; moderate: hospitalization for 4–10 days and severe: hospitalization for more than 10 days, or hemorrhagic pancreatitis, pseudocyst formation, or requiring intervention (percutaneous drainage or surgery) (Odes et al., 1977) .

Adverse effects of diclofenac and allopurinol which, include drug allergy, gastrointestinal bleeding and renal impairment, were evaluated during hospital stay and after discharge

Statistical analysis

Quantitative data were expressed as mean ± SD (Standard Deviation) while qualitative data were expressed as number and percent. Tests of significance used were: Student t-test: to measure the difference between two means of two different quantitative variables of two different groups. Paired t-test: to measure the difference between the same variable measured repeatedly within the same group. ANOVA test was used to measure the difference between more than two means of more than two different quantitative variables of more than two different groups.

3. Results

Over a period of 20 months from November 2004 to June 2006, 130 patients with obstructive jaundice were randomized into 4 studied groups with different modalities of therapy, demographic and laboratory data are shown in table (1).

Table (2) shows the different indications for ERCP in the study patients; the most common was CBD stones in 55 patients (42.3%), followed by biliary stricture in 52 (40%). Table (3) and Figures 1(A, B) show serum lipase and amylase in the study groups over time. Both were found to be significantly higher after 4 and 24 hours following the procedures in group (1) (patients who received diclofenac 100 mg suppository), group (2) (patients who received allopurinol 300 mg) and in group (4) (control group). In group (3) (patients who received allopurinol 600 mg), serum amylase was statistically higher after 4 hours and non significantly lower after 24 hours, while serum lipase was non significantly higher after 4 hours and non significantly lower after 24 hours compared to serum level immediately before ERCP.

As regard easy or failed cannulation of common bile duct, no significant relation to raised serum lipase and or serum amylase in different studied groups post ERCP as shown in table (3). Most common therapeutic interventions were biliary sphictrotomy, precut, stone extraction, dilatation of biliary stricture, biliary stent insertion and nasobiliary tube drainage. Serum amylase and lipase measured at 4 and 24 hours after ERCP were not significantly different regardless weather the ERCP procedure was diagnostic or therapeutic in the control, diclofenac, and allopurinol 300mg groups ($p>0.05$). While , they were significantly lower after 24 hours in patient undergoing therapeutic ERCP in allopurinol 600mg group ($p<0.05$)(Table 4).

The number of cases who had more than 3-fold increase in serum amylase and/or lipase was significantly higher in the control group, and was lowest in the high dose allopurinol group 8/20 (40%) in the control group; 5/30 (16.7%) in the 300mg allopurinol group; 5/40 (12.5%) in the diclofenac group and 4/40 (10%)) in the 600 mg allopurinol group [$p< 0.05$] (table 5). Out of these 22 patients who presented with more than 3 fold elevation of amylase and/or lipase, 3 patients had a clinical picture suggestive of acute pancreatitis (3/130 (2.3%),1/30(3.3%) in group who took 300 mg allopurinol and 2/20(10%) in control group , all the 3 cases were mild and improved by conservative treatment without any mortality.

Table 1. Pre-ERCP demographic and laboratory data of studied groups

	Group 1 (n=40)	Group 2 (n=30)	Group 3 (n=40)	Group 4 (n=20)
Sex (M:F)	25:15	16:14	24:16	14:6
Age	51.8±14.6	53.3±11.5	47.6±14.3	46.95±14.4
Bilirubin total	12.2±11.5	14.9±11.2	15.9±9.2	18.1±11.6
Bilirubin direct	9.2±9.1	11.4±9.2	11.9±7.1	14.2±10.1
Albumin	3.4±0.6	2.8±0.6	3.2±0.6	3.5±0.5***
ALT	156.8*±188.4	67.3±48.7	110±91.5	70.3±67.9
AST	104.9±109.7	75.5±95.4	87.5±57.2	60.4±29.2
GGT	306.4±240.8	175.3±111.9	354.5±321.3*	177.2±154.0
ALP	403.5±234.1	292.1±13	568.2±576.5*	339.0±216.0

Group 1: Diclofenac 100mg, group 2 : Allopurinol 300, group 3: Allopurinol 600mg, group 4: control group. * $P < 0.05$ in comparison to other groups, *** $P<0.001$ in comparison to other groups.

Table 2. Indications for ERCP in all patients.

Diagnosis	Total number = 130
• CBD stones	55 (42.3%)
• Biliary stricture o Benign causes o Cholangiocarcinoma	52 (40%) 12 (9.2%) 40 (30.8%)
• Ampullary adenoma	3 (2.3%)
• Pancreatic mass	16 (12.3%)
• Post operative biliary leak	4 (3.1%)

Table 3. Serum amylase and lipase before, 4 and 24 hours after ERCP.

Variable	Group	Immediately Before ERCP Mean ±SD	4 hours after ERCP Mean ±SD	24 hours after ERCP Mean ±SD	P1	P2	P3
Serum amylase U/L	**Diclofenac 100mg**	68.61±23	134.03±76.8	106.43±75.4	<0.001	<0.001	<0.001
	Allopurinol 300mg	70.9±25.5	177.5±146.1	143.6±190.9	<0.001	<0.05	<0.05
	Allopurinol 600mg	89.2±59.9	142.8±87.5	78±36.6	<0.001	>0.05	<0.001
	Control	57.72±23.12	231.4±107.8	172.5±147.4	<0.001	<0.001	<0.001
Serum lipase U/L	**Diclofenac 100**	76.9±42.13	130.6±106.1	122.9±119.8	<0.001	<0.001	>0.05
	Allopurinol 300	122±60.5	251.1±214.6	180.8±177.9	<0.05	<0.05	<0.001
	Allopurinol 600	109.6±99.2	150.2±143.8	90±59.2	>0.05	>0.05	<0.05
	Control	123.27±47.15	333.54±140	243.5±154.2	<0.001	<0.001	<0.001

P1= Comparison of serum amylase & lipase immediately before and 4 hours after ERCP.
P_2= Comparison of serum amylase & lipase immediately before and 24 hours after ERCP. P_3= Comparison of serum amylase & lipase 4 hours and 24 hours after ERCP.

Table 4. Serum amylase & lipase in those who had ERCP with and without therapeutic intervention in the studied groups immediately before, 4 and 24 hours after ERCP.

variable			N	Immediately before ERCP Mean ± SD	4 hours after ERCP Mean± SD	24 hours after ERCP Mean ± SD
Control group						
Amylase	Therapeutic intervention	+ve	16	57.6 ± 23.7	234.15±119.6	158.3± 147.8
		-ve	4	58.1± 23.6	220.4± 43.2	229.2± 151.6
Lipase	Therapeutic intervention	+ve	16	127.8± 44.9	345.2±115.1	232.4± 153.5
		-ve	4	108.2± 60.1	286.6 ± 72.2	287.4±117.1
Diclofenac100mg group						
Amylase	Therapeutic intervention	+ve	38	68.6± 23.6	137.6 ± 77.1	107.9± 76.9
		-ve	2	67.7± 3.2	64.7± 16.5	76.8± 31.8
Lipase	Therapeutic intervention	+ve	38	77.4± 43.1	134.3±107.6	127.1± 121.4
		-ve	2	66.1± 16.8	59.4± 1.2	42.4± 2.1
Allopurinol 300 mg group						
Amylase	Therapeutic intervention	+ve	18	65.4± 26.8	170.4± 150.6	139.2± 19.2
		-ve	12	76.9± 26.7	161.9± 100.3	117.8± 45.2

Lipase	Therapeutic intervention	+ve	18	119.7± 61.9	240.5±201.5	184.9± 180.1
		-ve	12	136.2± 30.1	289.6±229.5	170.1±68.4
Allopurinol 600 mg group						
Amylase	Therapeutic intervention	+ve	28	87 ± 53.2	139.1 ± 83.4	70.0 ± 24.6*
		-ve	12	90.2 ± 57.2.1	151.5± 100.1	96.7 ± 52.2
Lipase	Therapeutic intervention	+ve	28	106.5 ±89.3	133.2± 101.4	76.7 ± 51.1*
		-ve	12	112.4 ± 99.7	190.0 ± 21.4	121.1 ± 66.9

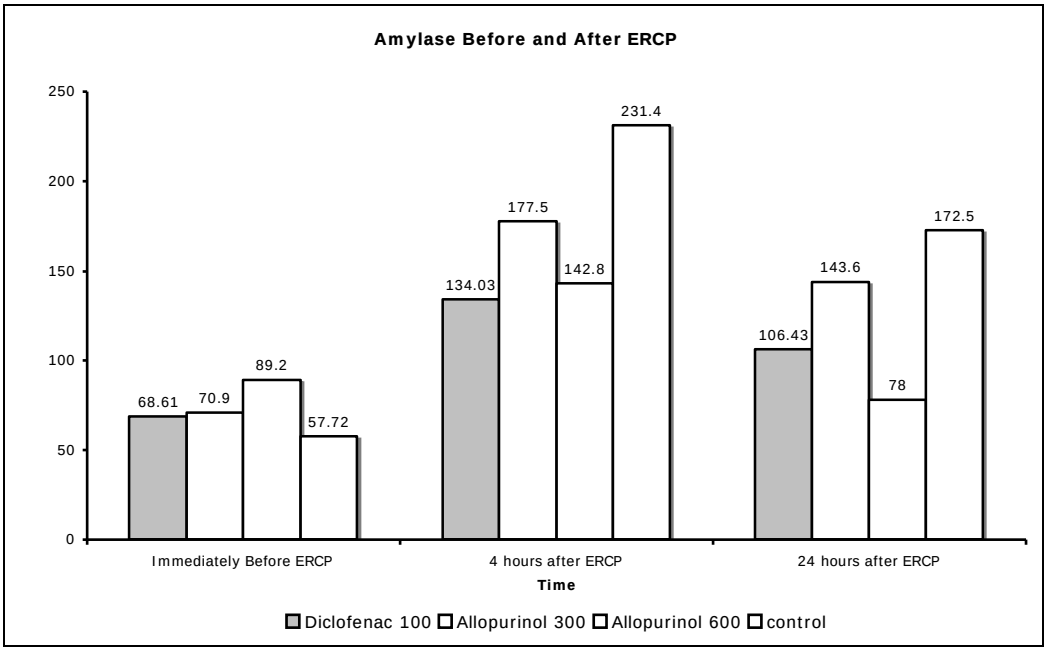
**P* < 0.05 serum amylase and lipase is significantly lower after 24 hours in patient undergoing therapeutic ERCP in large dose allopurinol group

Table 5. Comparison of the studied groups as regards the number of cases who had elevation of serum amylase and or lipase more than 3 folds normal.

			Groups				Total (n =130)	P – value
			Group 1 (n = 40)	Group 2 (n = 30)	Group 3 (n = 40)	Group 4 (n = 20)		
Cases who had elevation of amylase and or lipase more than 3 folds normal	+ ve	N0.	5	5	4	8	22	< 0.05
		%	12.5	16.7	10.0	40.0	16.9	
	- ve	N0.	35	25	36	12	108	
		%	87.5	83.3	90.0	60.0	83.1	

Group 1: Diclofenac 100mg, group 2 : Allopurinol 300, group 3: Allopurinol 600mg, group 4: control group.

A.



B.

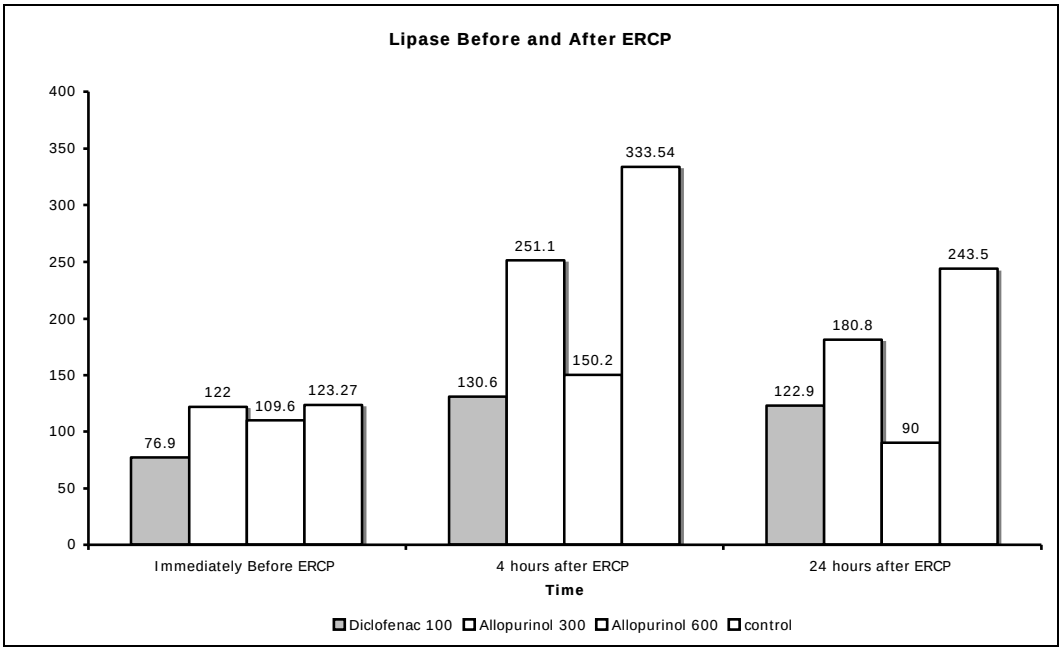


Figure 1 (A, B). Serum amylase and lipase before 4 and 24 hours after ERCP.

4. Discussion

There have been ongoing attempts to minimize the incidence and the severity of post-ERCP pancreatitis (Gottlieb and Sherman, 1998). This goal may be achieved in several ways by identifying high-risk patients in whom other methods of diagnosis and treatment should be considered before ERCP (Poon et al., 1999), by developing endoscopic interventions that can prevent or limit ERCP-induced pancreatic injury (Binmoeller et al., 1992) and by identifying a prophylactic pharmacologic agent that could be administered before, during or after the procedure (Hogan, 1998; Tarnasky et al., 1998; Testoni, 2004). Pharmacological prevention has been mainly addressed to: a) reducing the amount of intrapancreatic enzymes; b) preventing co-localization of enzymes and lysosomal hydrolases; c) blocking some steps of the enzyme-activated inflammatory cascade; d) reducing sphincter of Oddi (either biliary or pancreatic segment) post-procedure hypertension (Makela et al., 1997).

Although the exact mechanism(s) leading to post-ERCP pancreatic injury is unknown, there is great interest in pharmacologic treatment aiming to modulate the inflammatory mediators and activation of proteolytic enzymes thought to be involved in the development and the propagation of pancreatitis. Trials of prophylactic agents, including calcitonin (Odes et al., 1977), corticosteroid (Sherman et al., 2003), glucagons (Silvis et al., 1975) and nifedipine (Prat et al., 2002) failed to show benefits in prevention of post-ERCP pancreatitis. A meta-analysis of multiple, small, and sometimes contradictory studies involved somatostatin, its synthetic analog octreotide (both inhibitors of pancreatic secretion), and gabexate mesylate (a synthetic protease inhibitor) suggested that somatostatin and gabexate reduce the frequency of pancreatitis after ERCP (Andriulli et al., 2000). However, octreotide may, in fact, worsen ERCP-induced pancreatitis, presumably because of an increase in pancreatic sphincter pressure (Sternlieb et al., 1992).

The disadvantages of administration of somatostatin or gabexate include the need for prolonged intravenous infusion, problematic for patients undergoing outpatient ERCP, in addition to their high cost (Katsinelos et al., 2005). In view of the above-mentioned limitations, a drug that has minimal side effects, few contraindications to its use, inexpensive, acceptable to patients, with apparent prophylactic effect against post-ERCP pancreatitis is still needed. Hyperamylasemia is a frequent occurrence after ERCP (Poon et al., 1999; Barkin et al., 1991; Tittobello, 1997). Post-ERCP hyperamylasemia is known to peak between 90 min and 4 hours (Weiner et al., 1995). Therefore; it is hypothesized that the 4-hours amylase level which we used in this study, would be

most discriminatory for the prediction of subsequent pancreatitis (Panagiotis et al., 2005).

Phospholipase A2 (PLA2) is believed to play a key role in the initial inflammatory cascade of acute pancreatitis by regulating a number of proinflammatory mediators, including prostaglandins, leukotrienes, and platelet-activating factor (11). Inhibition of PLA2 has been the target of several agents used to treat non-ERCP-induced human acute pancreatitis with largely disappointing results. The role of these agents in the prevention of post-ERCP acute pancreatitis is more promising. Gabexate mesilate, a protease inhibitor, with activity that includes inhibition of PLA2, has been shown to prevent pancreatic damage related to ERCP and reduces the incidence of post-ERCP pancreatitis (Cavallini et al., 2006).

It has been shown that nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of PLA2 activity in the serum from patients with severe acute pancreatitis, (Makela et al., 1997). Diclofenac inhibits prostaglandin synthesis, it strongly inhibits neutrophil/endothelial attachment, thus preventing accumulation of neutrophils at the site of tissue damage, and it inhibits the expression of nitric oxide synthase, an enzyme associated with inflammation and cell damage. The peak concentration of diclofenac administered by suppository occurs between 30 and 90 minutes after administration (Moreto et al., 2003). NSAIDs have also been shown to have beneficial effects in experimental acute pancreatitis (Murray et al., 2003). Diclofenac 100 mg suppository administered immediately after the ERCP procedure, was proven effective in preventing post-ERCP pancreatitis in a single center human study (Moreto et al., 2003)

Studies in animal models 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 (Sanfey et al., 19984; Nordback andCameron, 1993; Nordback and Cameron,1993; Marks et al.,1984), It has been investigated previously using low dose in humans for prevention of post-ERCP pancreatitis with controversial results Clemens et al.,1991; Makela et al.,1997; Badra et al., 2000; Mosler et al., 2005). Allopurinol 300 mg prevented the increase in amylase and lipase more than octreotide (Badra et al., 2000). Clemens et al. 1991 and Budzynska et al, 2001) and the multicenter study by Mosler et al. 2005 found that 300 mg allopurinol did not reduce the frequency or the severity of post-ERCP pancreatitis. However, pretreatment with high-dose, orally administered 600 mg allopurinol has recently been shown to decrease the frequency of post-ERCP pancreatitis (Katsinelos et al., 2005).

In this study, there was significantly lower incidence of post-ERCP pancreatitis in diclofenac group in comparison to control group (40% had pancreatitis in the control group vs. 12.5% in the diclofenac group , $p< 0.05$) and this finding agrees with the results of Murray et al, 2003, who included 220 patients (110 received rectal diclofenac and 110 received placebo) and found that rectal diclofenac was shown to reduce the frequency of post-ERCP pancreatitis. In the regular dose allopurinol 300mg treated group, the findings of the present study revealed that there was non-significant lower incidence of post-ERCP pancreatitis compared to the control group (40% had pancreatitis in the control group vs. 16.7 % in the allopurinol 300mg group, $p> 0.05$).

We used the usual standard dose of Allopurinol (300 mg orally 1 hour before ERCP), this agrees with the following studies of Allopurinol in human which also used usual low dose of Allopurinol; Clemens et al, 1991 found that allopurinol did not reduce the frequency of pancreatitis or the degree of hyperamylasemia after ERCP,also Budzynska et al, 2001 found that the overall incidence of pancreatitis was 10.7 %, with 12 % in the prednisone group, 12.1 % in the allopurinol group, and 7.9 % in the placebo group ($p>0.05$). There were no statistical differences in the incidence or distribution of severity grades between the groups.

As regard higher doses of allopurinol (600 mg) in the present study, the number of cases with elevated serum amylase and /or lipase post-ERCP, was found to be significantly lower than those of control group ($p<0.05$) and it was non significantly lower than those in the diclofenac or low dose allopurinol groups ($p>0.05$).

In this study, three of the 22 patients who had post-ERCP more than 3 fold elevation of amylase and/or lipase developed a clinical picture suggestive of acute pancreatitis (2.3%), 1/30(3.3%) in the group who took 300mg allopurinol and 2/20(10%) in the control group. All the 3 cases were mild and improved by conservative treatment without any mortality. No case had clinical acute Pancreatitis in the diclofenac or high dose allopurinol groups.

we studied the relationship between some types of therapeutic intervention as potential risk factors and the occurrence of pancreatitis in all groups,

the studied types of therapeutic intervention were biliary sphincterotomy & stone extraction, biliary stent and nasobiliary tube and they were not risk factors in all groups (p>0.05). In agreement with our results, Freeman and Guda; 2004, stated that Biliary sphincterotomy and nasobiliary tube are not risk factors for post-ERCP pancreatitis.

In conclusions, we found that high dose allopurinol (600 mg) prevented the increase in serum amylase at 24 hours and serum lipase at 4, and 24 hours after ERCP. Both diclofenac and allopurinol 600 mg were associated with lower incidence of post–ERCP pancreatitis. We recommend that the efficacy of both diclofenac suppository and high dose allopurinol should be confirmed in further larger prospective multicenter studies before their routine clinical use can be recommended. Also we recommend evaluating high dose Allopurinol and Diclofenac in a trial which includes only patients with high risk for post-ERCP pancreatitis.

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