Research Article

Correlation between Allopurinol and Epinephrine in the prevention of post Endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis

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Abstract

This study was done to evaluate and investigate the effects of using different drugs on reducing the frequency and severity of Post- ERCP pancreatitis. The study was done on 90 randomized patients with extrahepatic cholestasis and divided into three groups. Post ERCP pancreatitis was diagnosed by laboratory investigations, ultra-sonography and triphasic abdominal CT criteria of pancreatitis. The results of this study showed that there was a statistically significant difference in the percentage of knife precut between the studied groups. There was a statistically significant difference in the degree of post ERCP pancreatitis during comparison the control group with each studied drug group, in which allopurinol has a protective role in the occurrence of post ERCP pancreatitis by regression analysis. It is concluded to use allopurinol before ERCP procedure.

Keywords: ERCP, pancreatitis, knife precut, Allopurinol.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most commonly performed endoscopic procedures. The recent shift towards interventional uses of ERCP is largely due to the emergence of advanced imaging techniques, including magnetic resonance cholangiopancreatography and ultrasonography [1].

ERCP is used primarily to diagnose and treat conditions of the bile ducts and main pancreatic duct, including gallstones, inflammatory strictures (scars), leaks (from trauma and surgery) and cancer [2].

Complications of ERCP can be broadly divided into short-term (within 3 days of the procedure) and long term (> 3 days after the procedure) complications. The reported incidence of ERCP-specific complications ranges from 5% to 40%, depending on the complexity of the procedure, the underlying diagnosis and patient comorbidities [3].

According to Cotton's criteria, acute pancreatitis which occurs after ERCP is diagnosed in patients who experience abdominal pain after the procedure with a concomitant $\geq$ 3 fold increase in blood serum amylase activity that persists 24 hours after ERCP and who require hospitalization [4,5].

Post ERCP pancreatitis is believed to be multifactorial involving a combination of chemical, hydrostatic, enzymatic, mechanical and thermal factors. Although there is some uncertainty in predicting which patients will develop acute pancreatitis following ERCP, a number of risk factors acting independently or in concert have been proposed as predictors of post-ERCP pancreatitis [6].

Allopurinol plays a part in the prevention of post-ERCP pancreatitis through the reduction of oxygen free radicals [7]. Topical application of epinephrine on the papilla may reduce papillary edema by relaxing the sphincter of Oddi or by decreasing capillary permeability. They are also inexpensive drugs for prevention of post-ERCP pancreatitis [8].

Patients & Methods

Patients:

This study was conducted on 90 randomized patients with extrahepatic cholestasis subjected

to ERCP. The patients were selected from tropical medicine department and general surgery department of EL-Minia University hospital. The patients were selected for this study according to the following inclusion and exclusion criteria:-

Inclusion criteria:
The patients of either sex; male or female, of age range from 27-78 years old and had to have extra-hepatic or intrahepatic biliary dilatation diagnosed by ultra-sonography and triphasic abdominal CT.

Exclusion criteria:
Patients with pancreatitis diagnosed by laboratory investigations, ultra-sonography and triphasic abdominal CT criteria of pancreatitis (e.g. enlargement of pancreas, inflammatory changes in pancreas and peripancreatic fat, ill-defined single peripancreatic fluid collection and two or more poorly defined peripancreatic fluid collections) were excluded.
The patients were divided into 3 groups as follow:
Group I (control group that included 30 patients): patients were not given any drugs before or after ERCP.
Group II (Allopurinol treated- group): included 30 patients, allopurinol (600mg) was taken orally one hour before ERCP.
Group III (Epinephrine- treated group): included 30 patients were given 20 ml of 0.02% epinephrine sprayed on the papilla during ERCP.

Methods:
all patients in this study were subjected to the following:

1- Full history taking
2- Full clinical examination 3- Laboratory investigations serum amylase (normal 25-125 unit per liter) [9]. The serum amylase level was evaluated before ERCP and 6, 24, 48 hours post-ERCP. INR, total leucocytic count, random blood sugar, liver function tests, blood urea and serum creatinine.

Endoscopic retrograde cholangiopancreatography (ERCP) technique: Before ERCP, the patients were prepared by fasting at least 8-12 hours and instructed regarding the associated medical history. They were instructed to stop concurrent used medication that lead to bleeding and correction of any bleeding tendency.

During ERCP, the patient lies on prone position and general anesthesia was performed under supervision of an anesthetist. ERCP was performed using Pentax EPM-3500, where side-viewing duodeno-scope is introduced to the stomach till the pylorus then passed to the duodenum and its papilla was visualized for mass or any abnormality.

Management was done according to the pathology as in case of calcular obstruction, stone extracted by ballon dilatation or mechanical lithotripsy followed by stent implantation. If large stone > 1cm, fragmentation of stone occurred by mechanical lithotripsy followed by stent implantation. After ERCP, the patients were followed up for possible complications by clinical examination and investigation.

Statistical analysis: The data were analyzed by SPSS (statistical package for social sciences) program version 24. The significance of differences for parametric quantitative data was calculated by using One-way ANOVA test. Kruskal Wallis test was used for non-parametric data. Fisher exact test was used to calculate the significance of qualitative data between the five groups. Univariate and multivariate regression analysis were used for predicting pancreatitis. For all tests, $P < 0.05$ was considered significant.

Results

Diagnostic and therapeutic ERCP were done to all studied patients with obstructive jaundice. **Table 1** showed indications of ERCP in all studied patients, 10 (11.1%) patients had stricture (4 patients in group I, 2 patients in group II, 4 patients in group III), 51 (56.7%) patients had calcular obstructive jaundice (18 patients in group I, 17 patients in group II and 16 patients in group III. Malignant obstructive jaundice occurred in 29 (32.2%) patients. It was diagnosed as cancer pancreas in 20 patients (5 in group I, 7 in group II, 8 in group III)

Hepatic focal lesions occurred in 3 patients (one patient in group I, 2 in group II) and enlarged porta hepatis, para aortic and pre pancreatic lymph nodes in 6 patients (2 in group I, 2 patients in group II, 2 patients in group III).

There was a statistically significant difference in diagnosis of causes of obstructive jaundice between studied groups **(table 1).**

Table 2 showed the details of ERCP procedure for all studied groups. The mean± SD of the procedure time in all groups was shown in this table. The least mean procedure time (min.) was in group II (12.5± 7.1) and the longest mean procedure time was in group III (20.1±9.3). All patients were received pre ERCP antibiotics. The least number of patients that underwent stone extraction was in group III (16 (55.53%) patients). The biggest number of patients was in group I (18 (60%) patients. Biliary stent insertion and biliary sphinctrotomy were done to all studied patients. Knife precut was done in 25 patients (9 in group I, 7 in group II and 9 in group III). There was a statistically significant difference in the percentage of knife precut between the studied groups.

Table 3 showed the incidence of post ERCP hyperamylasemia in control and all drug groups. It was found that there was no statistically significant difference in post ERCP serum amylase level at all different times in all groups. Epigastric pain occurred in 40 patients underwent ERCP (15 in group I, 12 in group II and 13 in group III). There was a statistically significant difference between all studied groups ($P < 0.05$) **(table 3).**

There was a statistically significant difference in the degree of post ERCP pancreatitis during comparison the control group with each studied drug group, in which, the degree of pancreatitis is statistically significant decreased after drug intake. Group II showed the least number of patients that developed post ERCP pancreatitis (12 Patients only) **(table 3).**

Univariate regression analysis was done to factors associated with post ERCP pancreatitis, only precut and drug intake Before ERCP are statistically significant by regression analysis to predict the risk factors and protective factors of post ERCP pancreatitis. Precut ERCP was a risk factor for the development of post ERCP pancreatitis (OR was 10.5 and 95% confidence interval (CI) was 4.6-23.7. Drug intake before ERCP has a protective role (OR <1). It was noticed that Allopurinol was the best drug which can decrease the incidence of occurrence of post ERCP pancreatitis (OR= 0.362& 95% CI was 0.074-2.121) **(table 4).** This finding was confirmed by multivariate regression analysis which revealed that combination of these 2 factors only that can predict or decrease the occurrence of pancreatitis (precut ERCP (OR= 22.3) which means it is a risky and drug intake especially Allopurinol that has the least OR in all drugs (OR=0.426) which also means it has a protective role in the occurrence of post ERCP pancreatitis **(table 5).**

Table (1): The ultrasonographic & abdominal triphasic CT and ERCP findings in all studied groups

Groups Procedure details	Placebo I N=30	Allopurinol II N=30	Epinephrine III N=30	P value
Procedure time (min.) Mean±SD	15.6± 9.1	12.5± 7.1	20.1±9.3	0.252
Pre ERCP antibiotics	30(20%)	30(25%)	30(25%)	0.584
Stone Extraction	18 (60%)	17 (56.6%)	16 (55.53%)	0.487
Biliary stent insertion	30(20%)	30(25%)	30(25%)	0.435
Knife precut	9(30%)	7(23.3%)	9(30%)	0.001*
Biliary sphinctrotomy	30(20%)	30(25%)	30(25%)	0.276

Fisher exact test for qualitative data between groups
*: Significant level taken at P value < 0.05

Table (2): Procedure details for all studied groups:

Patients groups / ERCP findings		Group I (N=30)	Group II (N=30)	Group III (N=30)	P value
Stricture		4 (13.3%)	2 (6.6%)	4 (13.3 %)	**0.01***
Calcular		18 (60%)	17 (56.6%)	16 (55.53%)	**0.001***
Malignant	**Hepatic focal lesion**	1	2	0	**0.01***
	Enlarged lymph nodes	2	2	2	**0.01***
	Pancreatic mass (cancer head of pancrease	5	7	8	**0.001***

Fisher exact test for qualitative data between groups
*: Significant level taken at P value < 0.05

Table (3): Incidence of post ERCP hyperamylasemia, Epigastric pain and degree of post ERCP pancreatitis in all studied groups

Groups **Parameters**	**Placebo I** **N=30**	**Allopurinol II** **N=30**	**Epinephrine III** **N=30**	**P value**
6h serum amylase level Range Mean ± SD Median	 (37-1020) 406.5±372.6 110	 (38-1150) 371.1±372 116.5	 (53-1250) 422.2±415.5 111.5	 0.676
24h serum amylase level Range Mean ± SD Median	 (53-1170) 465±438.3 101.5	 (51-1030) 366±357.6 111.5	 (53-1080) 436.2±426.9 111.5	 0.252
48h serum amylase level Range Mean ± SD Median	 (53-1090) 455.6±421.7 99	 (48-870) 328.8±319.5 94.5	 (53-985) 392.9±388.8 90	 0.104
Epigastric pain No Yes	 15(50%) 15(50%)	 18(60%) 12(40%)	 17(56.7%) 13(43.3%)	 ***0.028****
Degree of pancreatitis				
Absent	16(53.3%)	18(60%)	17(56.7%)	**0.001***
Mild	0(0%)	6(20%)	0(0%)	
Moderate	8(26.7%)	4(13.3%)	10(33.3%)	
Severe	6(20%)	2(6.7%)	3(10%)	

Kuskal Wallis test for non-parametric quantitative data between the five groups,
*: Significant level taken at P value < 0.05

Table (4): Univariate regression analysis of factors associated with post ERCP pancreatitis

Factors		PEP		Univariate analysis		P value
		No	Yes			
		N=51 (56.7%	N=39 (43.3 %)	OR	95% CI	
Age >60 year <60 year		19 (37.2%) 32 (62.7%)	17(43.6%) 22(56.4%)	0.347	0.124-0.303	*0.321*
Sex Male Female		22(43.1%) 29(56.9%)	15(38.5%) 24(61.5%)	*0.456*	0.312-1.345	*0.365*
Biliary sphinctrotomy Yes (90 patients)		51 (56.7%)	39(43.3 %)	0.347	0.453-0.675	0.467
Precut ERCP **N0.: 25(27.8%)**		3 (12%)	22(88%)	10.5	4.6-23.7	***<0.001****
Drug	**Allopurinol** Yes (30)	18(35.3%)	12(30.8%)	0.362	0.074-2.121	**0.01***
	Epinephrine Yes (30)	17(33.3%)	13(33.3%)	0.874	0.316-2.418	0.795

PEP: post ERCP pancreatitis; OR: Odds Ratio; CI: Confidence Interval
*: Significant level taken at P value < 0.05

Table (5): Multivariate regression analysis of factors associated with post ERCP pancreatitis

Factors		PEP		Multivariate analysis		P value
		No	Yes			
		N=51 (56.7%	N=39 (43.3 %)	OR	95% CI	
Precut ERCP **N0.: 25(27.8%)**		3 (12%)	22(88%)	22.3	8.2-25.6	***<0.001****
Drug	**Allopurinol** Yes (30)	18(35.3%)	12(30.8%)	0.426	0.25-2.98	**0.01***
	Epinephrine Yes (30)	17(33.3%)	13(33.3%)	0.815	0.232-2.861	0.549

PEP: post ERCP pancreatitis; OR: Odds Ratio; CI: Confidence Interval
*: Significant level taken at P value < 0.05

Discussion

ERCP is a direct contrast technique of the pancreaticobiliary system. It is useful in the diagnosis and management of diseases involving the pancreas and bile ducts such as stones, benign and malignant strictures and developmental anomalies. Also, intra-hepatic bile duct pathologies can be treated by ERCP using occlusion cholangiography. Pathology in the gallbladder and cystic duct abnormalities can be visualized by ERCP [12].

The major complication of an ERCP is the development of pancreatitis which can occur in up to 5% of all procedures. This may be self-limited and minor but may need hospitalization and rarely to be life-threatening. Those at additional risk for pancreatitis are younger patients, females, procedures that involve cannulation or injection of the pancreatic duct, patients with previous post-ERCP pancreatitis and those with sphincter of Oddi dysfunction [13].

The pathophysiology of PEP is not well explained. Mechanical, hydrostatic, chemical, cytokine, oxidative, enzymatic, allergic, thermal and microbiological factors have all been discussed as being its causes. PEP may result from mechanical trauma which causing injury to the papilla or pancreatic sphincter and leading to swellof the pancreatic duct and obstruction to the flow of pancreatic enzymes. [14,15].

Post-ERCP pain with marked elevation of serum amylase and/or lipase especially when the values are greater than 1,000 IU/L, it is strongly suggestive of pancreatitis. In cases of diagnostic doubt especially when severe pancreatitis is predicted, radiologic imaging should confirm the diagnosis. Early recognition of post-ERCP pancreatitis may be possible by evaluating serum amylase or lipase within a few hours of the procedure [16,17].

The degree of pancreatic inflammation and serum hyperamylasemia was decreased after pretreatment with allopurinol in pancreato-graphy induced pancreatitis [18].

Post-ERCP pancreatitis should be managed and treated as other causes of acute pancreatitis. This is sometimes complicated because it is difficult to distinguish mild from severe disease during the early stages of the disease. In acute pancreatitis, close monitoring for signs of organ dysfunction is essential. [19].

It was found that there was no statistically significant difference in post ERCP serum amylase level at all different times in all groups. Epigastric pain occurred in 40 patients underwent ERCP (15 in group I, 12 in group II and 13 in group III). There was a statistically significant difference between all studied groups ($P < 0.05$).

Univariate regression analysis was done to factors associated with post ERCP pancreatitis. Precut ERCP was a risk factor for the development of post ERCP pancreatitis (OR was 10.5 and 95% confidence interval (CI) was 4.6-23.7. Drug intake before ERCP has a protective role (OR <1). It was noticed that Allopurinol and Epinephrine can reduce the incidence of occurance of post ERCP pancreatitis but allopurinol was preferred than epinephrine in this study to decrease the incidence of occurrence of post ERCP pancreatitis (OR= 0.362& 95% CI was 0.074-2.121).

Contrary to the results of the current study is that mentioned by Kamal et al., [20] who reported that the incidence of PEP in indomethacin alone group was 6.4% as compared to 6.7% in the combination group. Severe PEP was found in 12% versus 16% of patients in the indomethacin alone and combination groups respectively. The combination of papillary spray of epinephrine and rectal indomethacin does not reduce the incidence of PEP compared to rectal indomethacin alone in high risk patients.

On the other hand, Xu et al., [21] studied 941subjects undergoing diagnostic ERCP and demonstrated a reduction in PEP incidence by epinephrine which sprayed directly on the papilla at the time of ERCP. Prevention of PEP was occurred through relaxation of the spincter of oddi and reduction of papillary edema by decreasing capillary permeability.

The results of this current study were agree with that mentioned by Akshintala et al., [22] who studied the beneficial effect of epinephrine in the prevention of PEP. Topical epinephrine could reduce the risk of PEP by 75% compared

to controls on sensitivity analyses (OR 0.25, 95% CI 0.06-0.66).

The present study is against with Hatamia et al., [23] who stated that 66 patients were randomized to the epinephrine group (group A), 68 cases to the indomethacin group (group B) and 58 individuals to the indomethacin-epinephrine group (group C).They concluded that the single application of epinephrine and the combination of epinephrine and indomethacin significantly reduced the risk of PEP.

General measures for prevention of PEP includes proper training of endoscopist, maintaining proficiency, adequate disinfection, avoidance of diagnostic ERCP, avoidance of repeated cannulation and injection of PD, careful use of electrocautery and avoidance of balloon dilation especially in higher risk patients such as younger patients who are anicteric [24].

The present results were not agree with this of Mosler et al., [25] who analyzed 701 patients. They were randomized to receive either allopurinol or placebo 4 hours and 1 hour before ERCP. The overall incidence of pancreatitis was 12.55%. It occurred in 12.96% of patients in the allopurinol group (and in 12.14% of patients in the control group. Prophylactic oral allopurinol did not reduce the frequency or the severity of post-ERCP pancreatitis.

There was significant reduction of post-ERCP pancreatitis by allopurinol (OR= 0.362& 95% CI was 0.074-2.121) when compared to epinephrine which in disagreement with those of Romagnuolo et al., [26] who studied 586 subjects. The crude PEP rates were 5.5% (allopurinol) and 4.1% (placebo) (95% confidence interval 2.1%-4.8%).

The results of the current study are not in accordance with the study of Bai et al., [27] who showed no significant difference in the incidence of post-ERCP pancreatitis between allopurinol treated and allopurinol untreated groups (8.9 vs. 9.7%, P=0.68, RR 0.86, 95% CI 0.42-1.77).

The current study is agree with Katsinelos et al., [28] who showed that the frequency of acute pancreatitis was significantly lower in the allopurinol vs the placebo group. The protective effect of allopurinol was also apparent in the diagnostic ERCP and the biliary sphincterotomy subgroups when the frequency of post-ERCP pancreatitis was analyzed after stratification by procedure.

Conclusion

Owed to our results in this current work, it is concluded that acute pancreatitis is the most common complication after ERCP. Also, it is concluded that precut ERCP was a risk factor for the development of post ERCP pancreatitis and dministration of allopurinol can decrease the incidence of PEP. And so, it is advised to give allopurinol before ERCP and make further scientific researches to find another drugs that can ameliorate post ERCP pancreatitis

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