

ROLE OF SERUM AMYLASE IN EARLY PREDICTION OF POST ERCP PANCREATITIS

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Abstract

Background: Our aim was to predict post ERCP pancreatitis early using serum amylase levels measured at 3hours and 48hours. Pancreatitis is one of the major complications after ERCP. Early identification of pancreatitis is essential. **Materials and Methods:** This study included 75 patients from Madurai Medical College during the study period of one year. Patients without evidence of pancreatitis before ERCP who had normal amylase levels and imaging were included in our study. Patients with history of acute and chronic pancreatitis were excluded. Serum amylase levels were measured 3hrs and 48hrs after ERCP. The reference range for the serum amylase was up to 80 IU/L. **Results:** In our study the incidence of early hyperamylasemia was 38.2% and PEP was 3.9%. Mean serum amylase in non-PEP group at 3hr and 48hr were 86.3±71.2, 70.41 ±71 and in PEP group at 3hr and 48 hours were 61.66±31.07, 209±123. Pain abdomen after 24hours and progressive increase in amylase levels more than two to three times the upper limit of normal at 48hours was statistically significant (p value < 0.05) with development of pancreatitis. **Conclusion:** Transient elevation of amylase levels occurs after ERCP but it does not predict Post ERCP Pancreatitis. Early normal serum amylase level after ERCP do not rule out the possibility of PEP. Serial Measurement of amylase values were needed for early prediction of post-ERCP pancreatitis. Patients with progressive rise in amylase levels and pain abdomen 24 hours after procedure needs close monitoring.

INTRODUCTION

ERCP has been widely used in treatment of biliary and pancreatic diseases.^[1] Pancreatitis is one of the major complications after ERCP.^[2-7] Its incidence varies from 5% to 10%.^[8-11] The mechanisms of Post-ERCP pancreatitis (PEP) are complex and not fully understood. The risk factors for post ERCP pancreatitis are young age, normal serum bilirubin level, suspected SOD, history of post-ERCP pancreatitis, failed or difficult cannulation, balloon dilatation of an intact sphincter, pre-cut sphincterotomy, pancreatic duct injection, Pancreatic duct guide wire placement, pancreatic sphincterotomy.^[12-16] Early identification of pancreatitis post procedure is essential. Serum amylase and serum lipase are used for the diagnosis of acute pancreatitis.^[17] Asymptomatic hyperamylasemia occurs after 35% to 70% of ERCPs.^[11,18,19] Serum amylase is used for the diagnosis of PEP. But there is still no clear standard amylase levels and time period which helps in the prediction of post ERCP pancreatitis. Post ERCP Pancreatitis is defined as, new or worsening

abdominal pain, serum amylase or lipase more than 3 times the upper limit of normal at more than 24hrs after ERCP and requirement of admission or prolongation of a planned admission.^[20]

MATERIALS AND METHODS

This study included 75 patients from Madurai Medical College during the study period of one year. Patients without evidence of pancreatitis before ERCP who had normal amylase levels and imaging were included in our study. Patients with history of acute and chronic pancreatitis were excluded. Serum amylase levels were measured 3hrs and 48hrs after ERCP. The reference range for the serum amylase was up to 80 IU/L. Serum amylase was measured using CNP-G3 method. ERCP-related procedures were carried out using a side-viewing duodenoscope. All procedures were done by experts. All ERCP procedures were done under General Anaesthesia.

Statistical Analysis

All Statistical analysis was done by SPSS software version 16. The results of continuous data are

presented as mean, Standard deviation, Median and inter quartile range (IQR) and categorical data as percentages. Shapiro wilks normality test was used for testing the normality of data. Since the data levels were in skewed distributed, Mann–Whitney U-test was used for inter group comparison of continuous variables. Qualitative difference of categorical variables was assessed using chi square test or Fisher’s exact test. The results with p value <0.05 were statistically significant. Predictability of risk factors associated with development of pancreatitis was assessed by bivariate logistic regression.

RESULTS

Basic characteristics of study population

In our study population majority of patients were aged between 30 years to 60 years (58.7%) and 60% (45 patients) were male and 40% (30 patients) were female. Patients underwent ERCP for common bile duct stones, benign biliary stricture and malignant

biliary obstruction. Benign bile duct obstruction was seen in majority of patients 72% (54 patients), which includes Choledocholithiasis with or without cholangitis, and benign biliary stricture. Malignant biliary obstruction was seen in 28% (21 patients) which was shown in Figure 1. About 11.8% (9 patients) had associated periampullary diverticulum. Difficult cannulation was encountered in 28.9% (22 patients) and inadvertent pancreatic duct cannulation was encountered in 14.5% (11 patients). Cannulation and stone extraction were feasible after needle knife sphincterotomy in 5.3% and balloon sphincteroplasty in 14.5% (11 patients). Common bile duct stones were retrieved in 19.7% (15 patients). Post-ERCP pancreatitis were encountered in 3.9% (3 patients) even though Hyperamylasemia was noted in 38.2% (29 patients). All patients who developed pancreatitis had pain abdomen and CT abdomen suggestive of pancreatitis. 2.6% developed mild pancreatitis and 1.3% developed severe pancreatitis. Basic characteristics of study population was shown in table 1.

Table 1: Basic characteristics of study population

Variables	Frequency(n)	Percent (%)
Age group		
≤ 30 yrs.	8	10.6
31-60 yrs.	44	58.7
> 60 yrs.	23	30.7
Sex		
Female	30	40
Male	45	60
Benign CBD obstruction	54	72
Malignant CBD obstruction	21	28
Periampullary diverticulum	9	11.8
Difficult cannulation	22	28.9
Pancreatic duct cannulation	11	14.5
Balloon sphincteroplasty	11	14.5
Needle knife sphincterotomy	4	5.3
Post ERCP pancreatitis	3	3.9
Mild pancreatitis	2	2.6
Severe pancreatitis	1	1.3
Hyperamylasemia	29	38.2

Comparison of risk factors between PEP and non-PEP group

In our study risk factors were compared between 2 groups PEP and non-PEP groups. In PEP group 33.3.70% were younger age, 66.70% were male patients. Benign biliary obstruction was etiological event in 66.7% and malignant biliary obstruction seen in 33.3%. All PEP patients had difficult cannulation, 33.3% had inadvertent pancreatic duct cannulation, 33.3% had undergone balloon sphincteroplasty, 33.3% had undergone pre-cut sphincterotomy in 33.3% and cholangiogram was done in 66.7% of PEP patients. Early hyperamylasemia at 3hr noted in 33.3% of PEP patients and late hyperamylasemia at 48hrs was universal all post ERCP pancreatitis patients (100%). The comparison of risk factors between the two groups is shown in Table 2. Comparison of risk factors associated with post-ERCP pancreatitis and non-PEP group showed difficult cannulation and hyperamylasemia at 48hours showed statistically significant association with post-ERCP pancreatitis. Patients who developed pancreatitis had pain abdomen and CT abdomen suggestive of pancreatitis which was statistically significant when compared to non-PEP group. 3hr post ERCP amylase levels, other risk factors, Preoperative bilirubin levels had statistically no significant association with PEP.

Table 2: Comparison of risk factors between PEP and Non-PEP groups

Variables	Non-PEP		PEP		Pvalue
	N	Percent	N	Percent	
Age					
≤ 30 yrs.	7	9.7	1	33.3	
31-60 yrs.	42	58.3	2	66.7	0.287
> 60 yrs.	23	31.9	0		

Sex					
Female	29	41.73	1	33.3	
Male	43	58.3	2	66.7	
Benign CBD obstruction	51	71.2	2	66.7	0.799
Malignant CBD obstruction	20	28.7	1	33.3	
Periampullary diverticulum	9	12.3	0		1
Difficult cannulation	20	26	3	100	0.022*
Pancreatic duct cannulation	10	13	1	33.3	0.379
Balloon sphincteroplasty	10	13	1	33.3	0.379
Needle knife sphincterotomy	3	4.1	1	33.3	0.152
Cholangiogram	24	33.3	2	66.7	0.274
Pain Abdomen	0	0	3	100	0.009*
3hours Amylase	28	38.4	1	33.3	1
48hours Amylase	16	21.9	3	100	0.009*
CT abdomen pancreatitis	0	0	3	100	0.009*

Distribution of amylase levels in PEP and non-PEP patients

Out of 76 patients 3 patients developed pancreatitis. Comparing the mean amylase levels with PEP and non-PEP group showed the following results. The Mean serum amylase in non-PEP group at 3hr and 48hr were 86.3 ± 71.2 , 70.41 ± 71 and in PEP group at 3hr and 48 hours were 61.66 ± 31.07 , 209 ± 123 . In our study comparison of serum amylase levels at 3hours and 48hours with pancreatitis showed significant association with 48hr amylase levels (p value < 0.05). 3hr serum amylase had no significant association with post-ERCP pancreatitis. Comparing the 3h, 48h amylase levels with both PEP and non-PEP group showed there is significant decrease in serum amylase at 48hrs in non-PEP group. In PEP group 48hrs mean serum amylase was elevated. If there is reduction in 48hrs serum amylase comparing to 3hr, it excludes the risk of PEP and patient can be discharged. Table 3. showed the distribution of amylase levels in PEP and non-PEP patients.

Table 3: Distribution of amylase levels in PEP and non-PEP

	Non-PEP		Post ERCP pancreatitis		p value
	mean	Median	Mean	Median	
3 hrs. amylase levels	86.3 ± 71.2	60 ± 54	61.66 ± 31.07	61	0.782
48 hrs. amylase levels	70.41 ± 71	50 ± 40.7	209 ± 123	150	0.003*

DISCUSSION

Pancreatitis is the most common complication of ERCP.^[8] The incidence of Post-ERCP pancreatitis ranges from 5% to 10%.^{5,10} Asymptomatic hyperamylasemia occurs after 35% to 70% of ERCPs.^[11,18,19] Trauma during ERCP causes regurgitation of amylase into blood but most have no evidence of pancreatic injury. The mechanisms that lead to PEP are complex and not fully understood, involving a combination of chemical, hydrostatic, enzymatic, mechanical, and thermal factors.^[14,21] We cannot predict which patient will develop pancreatitis because more number of risk factors whether they individually or in combination will cause pancreatitis. Risk factors of PEP are patient related and procedure related.^[20] Young age, female gender, difficulty in bile duct cannulation, pancreatic sphincterotomy, papillary balloon dilatation, prior ERCP-induced pancreatitis, and sphincter of Oddi dysfunction are risk factors for post-ERCP pancreatitis. Risk factors which cause pancreatitis and transient elevation of amylase levels after procedure were same except the age and sex. Because after the trauma which occurs during cannulation, whether the patient develop pancreatitis or not will depend on host factors.^[22] In a study done by Freeman et al., risk factors for pancreatitis were young age and female gender.^[23] Sphincter of Oddi dysfunction is common in young women, which leads to the development of pancreatitis.

Amylase levels elevation occurs immediately after procedure without pancreatitis. But patients with persistent elevation of amylase levels needs close follow up because they may progress to Pancreatitis.^[24] In our study, ERCP was done benign biliary conditions like common bile duct stones and benign stricture of which accounted for 72% of cases and 28% of patients were due to malignant common bile duct obstruction which includes periampullary growth and cholangiocarcinoma. In study done by Ito et al also ERCP was done more in benign conditions similar to our study. Another study in which 98 patients underwent ERCP of which 60.2% was choledocholithiasis without cholangitis. Hyperamylasemia was observed in 38.4% patients and PEP developed in 3.9%. Study by Ito et al showed similar incidence of post-ERCP pancreatitis occurred in 3.6%. Christofordis et al reported that Post-ERCP pancreatitis occurred in 3.3 % similar to our study and but hyperamylasemia in 16.5 % compared to 38.2% in our study. Mean serum amylase in non-PEP group at 3hr and 48hr were 86.3 ± 71.2 , 70.41 ± 71 and in PEP group at 3hr and 48 hours were 61.66 ± 31.07 , 209 ± 123 . But patients in PEP group 3hr hyperamylasemia were 33.3% and 48hr hyperamylasemia was universal. Patients with fall in amylase levels at 48hr post procedure when compared to 3hr amylase had less likelihood of developing pancreatitis. Ito et al reported that fall in amylase level at 6 h after ERCP suggests the less likelihood of post-ERCP

pancreatitis. Ito et al. reported that patients with amylase levels at 3 hours twice the upper limit of normal with progressive elevation at 6 hours developed post-ERCP pancreatitis. In our study young age and female sex had increased chances of developing post-ERCP pancreatitis which was not statistically significant. Preoperative diagnosis and bilirubin levels did not have association with PEP and hyperamylasemia. Difficult cannulation was defined if at least one of the 3 criteria was present, cannulation attempts lasting >5 min, 5 or more papilla contacts, or 2 guidewire passages into the pancreatic duct.^[25,26] Difficult cannulation is a risk factor for predicting pancreatitis or hyperamylasemia probably attributed to excessive local trauma and subsequent tissue edema.²⁷ Difficult cannulation leads to edema of the ampulla and sphincter spasm which obstructs the pancreatic juice flow and leads to pancreatitis.^[25] Difficult cannulation was noted in 100% in PEP group and 26% in non-PEP group and it was statistically significant. In a study by Freeman et al., the risk of post-procedure pancreatitis (42%) was high in females with normal serum bilirubin, suspected SOD and difficult biliary cannulation. In our study difficult cannulation, young age and female sex had increased risk of PEP. Difficult cannulation was associated with PEP and hyperamylasemia in our study. Inadvertent Pancreatic duct cannulation was associated with PEP.^[28] Pancreatic duct cannulation had increased risk of hyperamylasemia but no increased odds seen in PEP in our study. In study done by Nguyen et al., 823 ERCPs were included in this analysis of which 3.77% were complicated by PEP. The incidence of PEP was 8.4% among unintended PD cannulation which was statistically significant.^[29] In our study, Cholangiogram done patients had increased risk of PEP and early hyperamylasemia. Sitaraman, Lalitha M et al study showed that intraoperative cholangiogram had five times increased risk of PEP. In this study 116 patients included of which 9 patients developed pancreatitis.³⁰ In our study, Needle knife sphincterotomy was noted in one patient in PEP group. It had increased risk of PEP and late hyperamylasemia. In study done by Nguyen et al., needle knife sphincterotomy was also identified as a risk factor for PEP (p-value = 0.017). Balloon sphincteroplasty had increased risk of PEP in our study.^[31,32] After repeated attempts of biliary cannulation ampullary edema occurs and cannulation will be further difficult. So, procedure can be stopped and planned later. In cases of cholangitis or urgent biliary drainage, precut sphincterotomy can be tried and now endoscopic ultrasound guided rendezvous procedure can be tried.^[31,32] Christoforidis et al, showed that at 24 hours after ERCP, patients with elevated Serum amylase levels more than 4–5 times the upper limit of normal and presence of abdomen pain developed pancreatitis.^[22] In study done by Testoni et al two third of patients with elevated amylase levels more

than 5 times the upper limit of normal at 4 hours after ERCP developed pancreatitis. So amylase levels at 4 hrs after ERCP predicts the development of PEP.^[33] On the other hand, another study showed that pain and amylase levels at 24 hours predicts pancreatitis than early amylase levels. Our study showed that pain abdomen after 24 hours and progressive increase in amylase levels more than two to three times the upper limit of normal at 48 hours was statistically significant (p value < 0.05) with development of pancreatitis. Our study, however, had few limitations. First, our sample size is small. Second, since there were no particular time points for assessing serum amylase levels, and serial serum amylase levels were not monitored, late hyperamylasemia at 48 hr for detecting PEP is not useful. Third, we had association of some risk factors with PEP individually and also when additive, but they were not statistically significant. Fourth, we did not compare the risk factors between mild and severe post ERCP pancreatitis in our study. In literature most studies showed the predictive role of early serum amylase post procedure at certain point of time.

CONCLUSION

Transient elevation of amylase levels occurs after ERCP but it does not predict Post ERCP Pancreatitis. Early normal serum amylase level after ERCP do not rule out the possibility of PEP. Serial Measurement of amylase values were needed for early prediction of post-ERCP pancreatitis. Patients with progressive rise in amylase levels and pain abdomen 24 hours after procedure needs close monitoring.

Conflict of interest statement

The authors report no conflicts of interest.

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