Four Hours Post Endoscopic Retrograde Cholangiopancreatography Serum Amylase as A predictor for Post Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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Abstract

Background: Endoscopic retrograde cholangiopancreatography, uses a combination of both endoscopy and fluoroscopy for diagnosis and treatment of hepatobiliary disorders. ERCP is generally considered to be safe and effective. Post-ERCP complication rates vary widely depending on the complexity of the intervention and the individual patient. Acute pancreatitis is the most common complication following ERCP maneuver, which is reported to occur in 2–10% of patients overall (varying between 2–4% in low risk patients up to 8–40% in high-risk patients). *Aim:* The study is designed to evaluate the clinical significance of 4-hour post endoscopic retrograde cholangiopancreatography amylase level as an early predictor of post ERCP pancreatitis. This will help to decide when to admit or discharge patient following ERCP, to early diagnose and treat post ERCP pancreatitis and hence spare major hospital resources. *Patients and Methods:* This study is a prospective cohort study, conducted in the endoscopy unit in Suez Canal university hospital, including adult patients of both sexes eligible for ERCP, excluding patients with pre ERCP pancreatitis, previous ERCP or patients with renal failure. *Results:* This study included 86 patients candidate for ERCP of whatever indication excluding patients with pre-endoscopic pancreatitis. In this study pancreatitis occurred in 14 patients out of 86(16.3%). 4 hours serum amylase level was significantly higher in patients with post ERCP pancreatitis than in patients without post ERCP pancreatitis (P=0.001). 4hours post ERCP serum amylase is a significant predictor for early prediction of occurrence of PEP. *Conclusions:* Rising of serum amylase 4 hours post endoscopic retrograde cholangiopancreatography above 3.5 ULR is a significant predictor and patient with this level should be admitted and early treated

Key Words: ERCP, Pancreatitis, Amylase

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a technique which use of endoscopy and fluoroscopy for diagnosis and treatment conditions of the biliary or pancreatic ductal systems. Through the endoscope, the physician can see the inside of the stomach and duodenum, and inject a contrast medium into the ducts in

the biliary tree and pancreas so they can be seen on radiographs[1]. ERCP was used primarily for diagnosis and treatment of problems of the bile ducts and main pancreatic duct, including gallstones, inflammatory strictures (scars), leaks (from trauma and surgery), and cancer[1-3]. ERCP could be performed for diagnostic and therapeutic reasons, although the development of safer and relatively non-invasive techniques such as magnetic resonance cholangiopancreatography (MR-CP) and endoscopic ultrasound (EUS) has meant that ERCP is now rarely performed without therapeutic intent. Because ERCP has a potential risk of severe post ERCP complications than most other endoscopic procedures do, having an appropriate indication for its use is extremely important[4]. Acute pancreatitis is the most common complication of ERCP. According to a large, multicenter study the incidence of post- ERCP pancreatitis (PEP) approximately is 6.7%. Although most episodes of pancreatitis following ERCP are mild (about 90%), a small percentage of PEP (about 10%) may Complain of moderate or severe pancreatitis need to be admitted for long duration , intensive care unit admission and utilization of major hospital resources; patients of sever PEP have a high morbidity and mortality[5-8]. It is of importance that we accurately recognize which patients will develop PEP. Since most ERCP practice is performed on an outpatient basis, early assessment and evaluation of patients can allow early secured discharge of most patients post endoscopic procedures who will not develop PEP or just may develop mild symptoms that will be self-limited and no complications post ERCP. On the other hand, early identification of those patients who may develop moderate or severe PEP help decisions regarding admission to hospital and intensive management[9-11]. In addition, early diagnosis helps the use of tar-geted management that has the possibility to prevent or reduce inflammation of pancreas. Therefore, major efforts concentrate on trying to recognize predictors of post-ERCP pancreatitis that help in earlier detection and allow for reducing severity. Serum Amylase increases in reaction to manipulations during ERCP in the majority of patients[12-17]. Without pancreatitis, serum amylase levels peak at approximately 90 minutes to approximately 4 hours after ERCP procedure and return around normal levels within 48 hours after ERCP procedure[18-23]. Although Serum amylase level is frequently elevated in uncomplicated ERCPs, the speed and degree of elevation is to a great extent seen in patients who develop PEP. Consequently, this study was conducted to assess the value of serum amylase as a potential predictor of PEP[20-25]. In a study conducted by Testoni et al., serum amylase and lipase concentrations at 4 hours after ERCP were reported to be useful for predicting or ruling out post-procedure pancreatitis[20].

Subjects and Methods

This study is a prospective cohort study, conducted in the gastrointestinal endoscopy unit in Suez Canal university hospital, included 86 adult patients of both sexes, presented with either painful or painless obstructive jaundice candidate for ERCP excluding patient with pre endoscopic pancreatitis, or patients with renal impairment. All subjects were subjected to Clinical evaluation: History, Examination: (general and abdominal examinations), ERCP procedure after consent assignment. Post ERCP pancreatitis is defined as the presence of pancreatic-type abdominal pain severe enough to require hospital admission associated with levels of S. amylase 3 times the upper limit of normal occurring within 24 hrs after ERCP.

1- Before ERCP

History taking including Socio demographic data, indication of ERCP, chronic illnesses, drug history, history of allergy to drugs and contrast dye, previous ERCP, Previous pancreatitis and previous operations.

Clinical examinations: including general and abdominal examinations

Laboratory data including Complete blood count, ALT, AST, alkaline phosphatase, bilirubin, prothrombin time, creatinine, amylase, s. lipase.

Radiological data including Abdominal US, CT or MRCP to determine the cause of obstruction. ERCP procedure was done in gastrointestinal endoscopy unit under general anesthesia in prone or lateral positions and diathermy is connected. The number of cannulation trials, amount of contrast dye, sphincterotomy or precut sphincterotomy, bleeding, stent insertion, ballooning dilatation, stone extractions, radiological diagnosis were recorded

2- After ERCP

Four hours after ERCP procedure, amylase was measured. While 24 hours post ERCP the following was assessed: complete blood count, ALT, AST, alkaline phosphatase, bilirubin, prothrombin time, creatinine, amylase, lipase. abdominal US or CT was done for patients with complications.

After patient stabilizations, patients were discharged.

Results

This study was conducted in the endoscopy unit Suez Canal university hospital and included 86 adult patients of both sexes excluding patients with previous ERCP, patients with pre-endoscope pancreatitis and patients with renal failure about 53 % of them were females. Most of their ages were less than 60 years (64%). Pancreatitis occurred in 16.3% of patients. The demographic, clinical, laboratory and ERCP findings are shown in the following tables. Most of study populations presented with evidence of extra hepatic biliary obstructions with jaundice either painless obstructive jaundice 54/86 (62.8%) or painful obstructive jaundice 32/86 (37.2%). In this study 14/86 patients (16.3%) were diagnosed to have post ERCP pancreatitis 24 hours post procedures. The prevalence of hyperamylesemia in both patients with and without pancreatitis revealed that 92.9 % of patients with post ERCP pancreatitis have significantly higher elevation of serum amylase level 4 hours post endoscopic procedure compared to 37.5 % only of patients without post ERCP pancreatitis (*p*=0.001) (Table 1).

Table 1: prevalence of hyperamylesemia in both patients with and without pancreatitis

4 hrs post ERCP serum amylase	Post ERCP pancreatitis		total	P value
	No	Yes		
Above ULN	27 (37.5%)	13 (92.9%)	40 (46.5%)	0.001
below ULN	45 (62.5%)	1 (7.1%)	46 (53.5%)	
Total	72(100%)	14 (100%)		

ULN= upper limit of normal

Univariate analysis of risk factors of post ERCP pancreatitis including sociodemographic data, pre endoscopic radiological and laboratory results and steps of endoscopic procedure shows a statistically significant associations between the increased risk of post-ERCP pancreatitis and pre endoscopic levels of AST and 4 hours post ERCP S. amylase (p=0.003, 0.000 respectively) and also with GB radiological findings (Table 2). ROC curve was used to define the best cut off value of the post

ERCP amylase which was ≥338μ/L, with sensitivity of 93.3%, specificity of 94.4%, PPV of 77.8%, NPV of 98.5% with diagnostic accuracy of 90.8% (Fig. 1) and Tables (3,4).

Table 2: Univariate Analysis of Risk Factors for Post-ERCP Pancreatitis in our study

| Variable			Post-ERCP pancreatitis		P value
			No (n=72) 83.7%	Yes (n=14) 16.3%	
Age (yrs)			51.18± 16.76	44.36± 14.71	0.736
Sex	Male		39 (54.2 %%)	4 (28.6 %)	0.080
	Female		33 (45.8%)	10 (71.4%	
Complain	Biliary Colic		28 (38.9%	4 (28.6%)	0.340
	Obstructive Jaundice		44 (61.1%	10 (71.4%	
ERCP Diagnosis	Calcular		54 (75.0%)	9 (64.3%)	0.465
	Malignant		15 (20.8%)	4 (28.6%	
	Biliary mud		1(1.4%)	1 (7.1%)	
	Unknown		2 (2.8%)	0 (0.0%)	
HB (pre endoscopic)			12.63±1.68	11.5357± 1.50	0.954
TLC (pre endoscopic)			8.0333± 3.39	8.21± 3.58	0.899
PLT (pre endoscopic			260.11± 102.94	301.71± 126.06	0.351
ALT (pre endoscopic			141.06± 118.77	124.50± 92.50	0.480
AST (pre endoscopic)			128.75 ± 90.1	106.86± 35.62	0.003
T. Bilirubin (pre endoscopic)			8.47± 7.11	6.6743± 4.95	0.412
D. Bilirubin (pre endoscopic)			6.29 ± 5.79	5.61± 4.55	0.659
PT (pre endoscopic)			12.43 ± 1.47	12.46 ± 2.36	0.084
Amylase (pre endoscopic)			56.04 ± 32.07	50.07 ± 25.80	0.81
Lipase (pre endoscopic)			41.03 ± 24.97	31.13 ± 20.72	0.38
Creat (pre endoscopic)			0.84 ± 0.21	0.83 ± 0.46	0.081
US of GB	Normal		11 (15.3%)	8 (57.1%)	0.002
	Chronic calcular cholycystitis		58 (80.6%)	5 (35.7%)	
	removed		3 (4.2%)	1 (7.1%)	
U/S CBD	Diameter		13.17±4.27	14.64±6.48	0.065
	Stones	Yes	27 (37.5%)	4 (28.6%)	0.524
		No	45(62.5%)	10(71.4%)	
US of liver span			14.07 ± 2.08	14.93 ± 1.07	0. 060
US of spleen span			10.76 ± 2.12	10.93 ± 2.25	0. .869
Cannulation			4.94± 2.63	6.86± 4.19	0.043
amount of contrast			16.27± 4.74	15.64± 3.41	0.101
Sphincterotomy	Yes		70 (97.2%)	14 (100%)	0. .528
	No		2 (2.8%)	0 (0%)	
Stent insertion	Yes		54 (75.0%)	10(71.4%)	0.779
	No		18 (25.0%)	4 (28.6%)	
Balloon sweeping	Yes		37 (51.4%)	7 (50.0%)	0.924
	No		35(48.6%)	7(50.0%)	
Stone Extraction	Yes		28 (38.9%)	6 (42.9%)	0..781
	No		44 (61.1%)	8 (57.1%)	
Amyase (4h Postoperative)			133.06± 140.53	641.43 ± 624.70	<0. .000
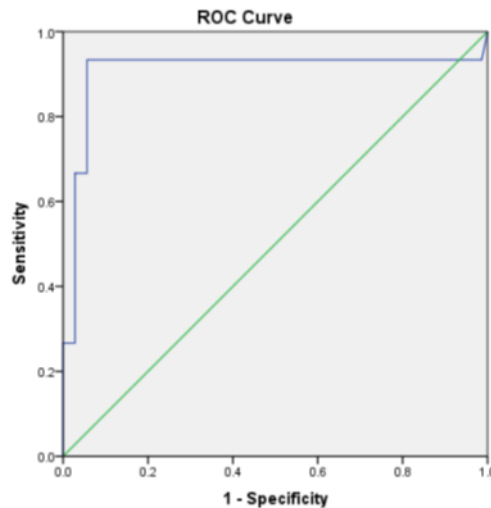
Figure 1: ROC curve for defining the best cut off value of the post ERCP amylase

Discussion

Endoscopic retrograde cholangiopancreatography is a very important maneuver in the diagnosis and management of different pancreato-biliary diseases. Despite all the advances and improvement in ERCP techniques, post-ERCP acute pancreatitis remains the most feared and common complication, being associated with high morbidity and mortality[26-28]. We aimed in our study to evaluate the clinical significance of 4-hour post endoscopic retrograde cholangiopancreatography amylase level as an early predictor of post ERCP pancreatitis. This study was conducted in endoscopy unit Suez Canal University hospital and included 86 adult patients of both sexes, excluding patients with pre endoscopic pancreatitis, history of previous ERCP and patients with renal failure, range of age in study population was between the 21 – 83 years, mean of 50.07 ± 16.55 years, most of their ages were less than 60 years (64%), about 53.5 % of them were females, about 89.5% of them were married, and about 67.5% of them lived in urban area. In this study post ERCP pancreatitis occurred in 14 patients out of 86 patients (16.3%). However., in a study in El-Mansoura university the overall, PEP occurred in 10.2% of patients[27]. Moreover in a meta-analysis of 108 randomized, controlled trials (RCTs) an overall incidence of post ERCP pancreatitis is 9.7%, with a mortality rate of 0.7% was reported[11].

Table 3: statistical significance of 4 hours post ERCP amylase level in prediction of acute pancreatitis at cut off point ≥338

Test	Value	P Value
Sensitivity	93.3% (95% CI: 68.1% - 99.8%)	< 0.001
Specificity	94.4% (95% CI: 86.2% - 98.4%)	< 0.001
Accuracy	90.8% (95% CI: 78.2% - 100%)	< 0.001
St. error	0.64	----
Positive predictive value	77.8% (95% CI: 57.2% - 90.2%)	< 0.001
Negative predictive value	98.5% (95% CI: 91% - 99.8%)	< 0.001
Positive likelihood ratio	16.57	----
Negative likelihood ratio	0.07	----

Table 4: 4h post-ERCP serum amylase utility in predicting post-ERCP pancreatitis

Amylase	Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio
> 2.5	92.9%	87.5%	59%	98.5%	7.4
> 3.5	**92.9%**	**93.1%**	**72.8%**	**98.5%**	**13.4**
> 4.5	64.3%	95.8%	75%	93.2%	15.4
> 5	57%	97.2%	80%	92.16%	20.5

In our study about 92.9 % of patients with post ERCP pancreatitis have elevation of serum amylase level 4 hours post endoscopic procedure compared to 37.5 % only of patients without post ERCP pancreatitis and this is statistically significant. In this study univariate analysis of risk factors of post ERCP pancreatitis including socio-demographic, indications, pre endoscopic laboratory and radiological finding and steps of endoscopic procedure and also 4hours post ERCP serum amylase revealed that statistically significant associations between an increased risk of post-ERCP pancreatitis and pre endoscopic levels of AST, and 4 hours post ERCP serum level of amylase. In our study 4hours serum amylase level was significantly higher in patients with post ERCP pancreatitis than in patients without post ERCP pancreatitis (P value 0.001) and this indicate that 4hours serum amylase level is a good predictor of post ERCP pancreatitis .Moreover it was concluded that the 4-h post-ERCP serum amylase level was found to be a useful means of predicting pancreatitis both after diagnostic ERCP and after therapeutic ERCP in a large retrospective study in a single center and this support our results. Also Testoni et al., in their study of twenty-four-hour Serum amylase predicting pancreatic reaction after endoscopic sphincterotomy showed that serum amylase assessment four hours after sphincterotomy is a reliable, cost-effective follow-up and minimizes the likelihood of underestimating the risk of post-procedure pancreatic reaction[29-31]. In our study according to ROC curve anal

ysis of 4 hours post ERCP amylase level, it was found that the cut off value of 4 hours post ERCP serum amylase level is >338 IU/L. at this amylase level more than or equal 338 the incidence of acute pancreatitis increases with sensitivity 93.3 %, specificity 94.4 %,positives predictive value (PPV) 77.8%, and negative predictive value (NPV) 98.5 with p-value <0.00. In another study conducted by Okasha et al., in Cairo university in 2015, they found that ROC curve analysis it was found that the cut off value of 4 hours post ERCP serum amylase level is >260 IU/L. at this amylase level more than or equal 260 the incidence of acute pancreatitis increases with a sensitivity of 88.89%, specificity of 94.51%, positive predictive value (PPV) of 61.50%, negative predictive value (NPV) of 98.9% and accuracy of 92%. p-value <0.001[26]. In this study 4 hours post ERCP serum amylase level is significant predictor of post ERCP pancreatitis at cut off value 3.5 ULR with sensitivity 92.9%, specificity 93.1% , positive predictive value 72.8%, negative predictive value 98.5% and Positive likelihood ratio 13.4. In a retrospective study Sutton et al. also studied the significance of post ERCP serum amylase level in prediction of increase risk of acute pancreatitis and they put a cut off value of 2.5 of upper limit range in case of pancreatogram with sensitivity 80% and specificity 80.4% and a cut off value of 5 of ULR in case of no pancreatogram with sensitivity 100% and specificity 91.8%[12-19]. In a study of 4 hours post ERCP serum amylase level as predictor of post ERCP pancreatitis in Australia the performance of the test at various cut-off

values, illustrating optimal sensitivity at a cutoff value 1.5-fold the normal level, and optimal specificity at a cut-off value three-fold the normal level[6-8]. In one study the optimal cutoff values for amylase were five times (625 IU/l) the upper limit of the normal range[23].

Conclusion

We can conclude that 4hours post ERCP serum amylase is a significant predictor for early prediction of occurrence of PEP. Rising of serum amylase 4 hours post ERCP ABOVE 3.5 ULR is significant predictor and patient with this level should be admitted and management of PEP should be rapidly started

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