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Original Research Paper

Surgery

CORRELATION OF BIOCHEMICAL PARAMETERS AND BILIARY ETIOLOGY IN ACUTE PANCREATITIS

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ABSTRACT

INTRODUCTION: Acute pancreatitis is common disease presenting in emergency department. Biliary calculus and alcohol consumption are most common etiologies. Detection of biliary etiology is important because the endoscopic retrograde cholangiopancreatography associated with endoscopic sphincterotomy can prevent further complications in patients with severe biliary pancreatitis and also in order to provide definite management in form of cholecystectomy to prevent further attacks. The majority of patients experience a mild course of the disease, with no need for immediate invasive intervention.In order to aim for early endoscopic decompression early detection of gallstones and determination of the severity of acute pancreatitis is essential. Differences in biochemical investigations of acute biliary and non-biliary pancreatitis have been observed and have been used to project the etilogy of pancreatitis.

OBJECTIVES: To find out and compare biochemical parameters in acute biliary and non-biliary pancreatitis and to correlate the parameters with the biliary etiology

METHODS: It is a prospective study carried out in Bir Hospital for 1 year and 3 months period. All admitted cases of AP were included in the study. Data analysis was done using SPSS 20.Fifty nine patients admitted with diagnosis of acute pancreatitis from October 2013 to December 2014 were included in the study. The relation between etiology with age, sex, admission serum amylase and total bilirubin. direct bilirubin, AST, ALT, ALP, LDH, serum amylase were evaluated.

RESULTS: Out of 59 patients 38(64.4%) and 21(35.6%) had biliary and non-biliary etiology respectively. Biliary pancreatitis was distributed more in females but not significant (16 vs 22). Distribution of severity was comparable between both groups. Biliary pancreatitis group had significantly higher amylase level(2032 IU vs 855IU, p 0.002) whereas values of liver function test were higher in biliary pancreatitis though not statistically significant.

CONCLUSIONS: A simple and approximate prediction of biliary etiology of acute pancreatitis can be obtained from biochemical parameters especially serum amylase.

KEYWORDS : biliary, amylase, acute pancreatitis,severity

INTRODUCTION

The two major causes of acute pancreatitis are biliary calculi, which occur in 50–70% of patients, and alcohol abuse, which accounts for 25% of cases. The remaining 10 to 20 % is accounted for either idiopathic disease or by a variety of miscellaneous causes including trauma, surgery, drugs, heredity, infection and toxins. The disease may occur at any age, with a peak in young men and older women. Gallstone pancreatitis is thought to be triggered by the passage of gallstones down the common bile duct. Serum amylase is most commonly used as a biochemical marker of acute pancreatitis (AP).[1]

Pain is the cardinal symptom. It tends to be moderately to intensely severe and tends to last for several days.[2] In alcoholic pancreatitis ,initial symptoms include vomiting as well as acute abdominal pain, which may be localized to the back and upper abdomen and is relieved by leaning forward.[3]

METHODS A study was conducted in NAMS Bir Hospital, Kathmandu.Those patients with diagnosis of first episode of acute pancreatitis will be included in the study. Written informed consent was taken from the patient.

The demographic data for all patients directly admitted to our institution with a diagnosis of acute pancreatitis between October 2013 and December 2014 were collected for this study. All patients transferred from outside institutions were also included. Data for all patients were prospectively collected for 7 days or until discharge if fewer than 7 days. This study was approved by the NAMS Institutional Review Board.

Acute pancreatitis was defined as 2 or more of the following: characteristic abdominal pain; serum amylase and/or lipase levels 3 times the upper limit of normal; and a contrast enhanced computed tomography scan of the abdomen or magnetic resonance imaging within the first 7 days of hospitalization demonstrating characteristic changes of acute pancreatitis. Patients with radiographic evidence of chronic pancreatitis were excluded from the study. Diagnosis of biliary and alcoholic pancreatitis was confirmed by presence of gall stones on AUS and history of alcohol intake without gall stones respectively. Patient without any identifiable cause were labelled as idiopathic pancreatitis.

Systemic inflammatory response syndrome (SIRS) was defined as 2 or more SIRS criteria. SIRS scores were calculated for all patients during first 7 days of hospitalization based on the most extreme laboratory value or clinical measurement in each 24 hour period.

SIRS was defined as transient if 48 hours or persistent if 48 hours during the first 7 days of hospitalization. The number of SIRS criteria (0 – 4) for each patient was determined during day 1. SIRS scores were calculated for all patients during first 7 days of hospitalization based on the most extreme laboratory value or clinical measurement in each 24 hour period.

Organ failure was defined as a score of 2 in 1 or more of the 3 organ systems described in the Marshall score. Organ failure was assessed for all patients during the first 7 days of hospitalization based on the most extreme laboratory value or clinical measurement in each 24 hour period.

Each patient was examined clinically and blood was sent for complete blood count,random blood glucose, serum urea, serum creatinine, serum electrolytes, serum amylase if not performed before, serum total bilirubin direct bilirubin, AST, ALT, ALP, LDH, serum calcium.ABG was done for every patient. All the patient were subjected to ultrasound of abdomen as it was easily available and accessible. Those who were classified moderately severe AP and severe AP were treated in intensive care unit with standard protocol.

Their CT findings were noted if done elsewhere or adviced if not done previously.

Severity of pancreatitis was classified as per revised Atlanta Classification, as mild acute pancreatitis, moderately severe pancreatitis and severe acute pancreatitis.

Chi square test and other statistical tests were used two compare parametric and non-parametric variables between two groups. SPSS 20 was used to analyse the data. P value <0.05 was considered significant.

RESULTS

Gender distribution of disease

A total of 59 patients who met the inclusion criteria were included in this study. None of the patients were excluded from the study.31 patients (52.5%) were females and 28(47.5%) were males. The patients were divided into two groups; biliary and non biliary. Overall prevalence of the disease had been seen more in female and also biliary pancreatitis was more in females but not significant (p=0.202).Eventhough disease occurred more in females it was not significant in the study(p=0.27).

Table 1 Sex distribution of the disease

		Gender		
		Male	Female	Total
Category	Biliary	16	22	38
	Non biliary	12	9	21
Total		28	31	59

Age distribution of the disease

Among the patients included in the study one patient was below 15 years 43 patients were between 16 to 65 years and 15 patients were above 65 years of age.Most of patients were of young age group and middle aged patients.AP was unusual in children.

Table 2.Age distribution of the disease.

Age	Biliary			Non biliary			Total
	M1	M2	S	M1	M2	S	
<15	1	0	0	0	0	0	1
16-40	12	2	0	4	2	1	21
41-64	9	3	1	6	2	1	22
>65	11	1	0	2	1	0	15

M1-mild AP

M2-moderately severe AP

S-Severe AP

Severity distribution of the disease

Among the two groups ,the distribution of the severity of the disease was comparable and also the severity of the disease distributed among the male and female patients was comparable. The severity of the disease was not seen correlated with the sex

Etiology

Gallstones and alcohol comprised the cause in about 85 percent of the patients.Other 15 percent comprised the rest.

Table 3.Etiologies of acute pancreatitis

Etiology	No.	Percentage
Biliary	38	64.4
Non biliary	21	35.6
Alcohol	12	20.4
Trauma	2	3.4
Idiopathic	7	11.8
Malignancy	0	0

Disease severity among biliary and non biliary patients

The severity of the disease in both the groups were comparable.As the number of patients were bigger in biliary group,there were more number of patients with mild acute pancreatitis while severe cases almost comparable.

Correlation of serum amylase and disease severity

Means of serum amylase of acute mild and acute moderately severe pancreatitis was not found to be significant. (p=0.14).So serum amylase did not correlated with the severity of the disease.

Comparision of means of different biochemical parameters by t test

Means of total bilirubin, direct bilirubin, AST, ALT and ALP were higher in biliary group but could not reach statistically significant level. However mean of serum amylase was significantly higher in biliary group.

Table 4. Comparision of the means of biochemical parameters in biliary and non biliary group

Paramtres	Biliary	Non biliary	P value
Total bilirubin	2.53	1.57	0.10
Direct bilirubin	1.49	0.93	0.17
AST	138	107	0.36
ALT	156	95	0.10
ALP	280	170	0.49
LDH	492	464	0.48
amylase	2032	855	0.002

DISSCUSION

The diagnostic sensitivity and specificity of serum amylase are higher in cases of acute biliary pancreatitis. The early detection of gallstones in acute pancreatitis by standard imaging techniques may be misleading; ultrasonography fails to identify the gallbladder in almost one-third of patients. Their lack of specificity prohibits their use as the sole means of detecting gallstones, but they may allow the selection of patients who require further investigations.[4] Those whose serum amylase was low usually alcoholic patients or presented late, had to be subjected to serum lipase and further radiological investigation.

In a study conducted by Gumaste VV et al found serum amylase values in group A(non biliary) ranged from 104 to 2985 U/L (median, 331 U/L) and in group B(biliary) from 423 to 13,000 (median, 1187 U/L). Although these figures were statistically different (P less than 0.005).[5]

In one other study the initial serum amylase value was higher in Group A patients and decreased more rapidly to a lower value than in Group B patients. It was concluded that both the initial value and pattern of serum amylase decay distinguish the hyperamylasemia of biliary tract disease from that of alcoholic pancreatitis.[6]

Nordestgaard et al found the mean serum amylase level was significantly different between patients with alcoholic pancreatitis (439 +/- 302 U/L) and gallstone pancreatitis (2,480 +/- 1,575) (p less than 0.001). However there is no correlation between the initial serum amylase level and the extent of pancreatic involvement visualized by CT.[7]

As serum amylase was readily available and cheap method of

diagnosing AP,it was done in every patient despite its lack of specificity.In this study serum amylase is significantly different in between the two groups.Although the serum amylase is the cornerstone laboratory test used in establishing the diagnosis of acute pancreatitis, there are limitations in the sensitivity and specificity that may be important for the clinician to recognize.[8]
Steven C. Kazmierczak, Paul G. Catrou et al have investigated biochemical markers, including AST, ALT, ALP, gamma glutamyltransferase, and total bilirubin.ROC analysis and the ROC AUC showed that the best classification of patients with respect to a biliary pathogenesis of acute pancreatitis occurred with ALT and AST at both initial and peak activities.In the current study also even though the means of the ALT, AST, ALP, total bilirubin and direct bilirubin and LDH were higher in biliary group than in non biliary group but they could not reach at significant level. These discrepancies in the study may be due, in part, to the timing of the collection of blood samples in which these analytes are measured.The rapidity of changes in the biochemical markers of pancreatic and hepatobiliary damage in patients with pancreatitis due to biliary obstruction make frequent serial testing imperative for accurate diagnosis.

Some studies have found these markers helpful in discriminating biliary from nonbiliary pancreatitis, whereas others have found them of limited diagnostic utility.Previous studies attempting to differentiate biliary from nonbiliary pancreatitis through biochemical indices have been retrospective, and the individuals included in these studies had only limited numbers of biochemical determinations performed.However, acute pancreatitis develops in only 4-8% of patients with cholelithiasis.Factors that may predispose some patients with gallstones to pancreatitis include the number and size of gallstones in the gallbladder and the anatomy and motor function of the biliary tract.

ALT has been correlated to biliary etiology in most of the studies. It is the most commonly used to predict biliary etiology and is thought to be the most useful of the available biochemical investigations in predicting gall stone etiology of AP and variable level of ALT has been identified with Positive Predictable value (PPV) between 98 to 100%.However in current study ALT levels was higher in biliary group but not statistically significant (156 U/L vs 95U/L, P=0.1). Above reasons might be explained for this discrepancy.

Tenner et al studied using receiver operating characteristic curves for each of the four parameters, and determined that the ALT level was the most clinically useful parameter. The higher the serum level of ALT, the greater its specificity and positive predictive value in diagnosing gallstone pancreatitis. At ALT levels greater than or equal to 150 IU/L (approximately a 3-fold elevation), the probability of gallstone pancreatitis was 95%.[9] Aspartate transaminase levels was nearly as useful as ALT. Their analyses of total bilirubin and alkaline phosphatase serum levels indicate that these tests were not useful in the diagnosis of gallstone pancreatitis.An increased serum level of alanine aminotransferase (>1.0 microkat/l) is associated with a high probability of gallstone pancreatitis (positive predictive value 80-90%).[10]

Systemic inflammatory response syndrome is the clinical manifestation of the inflammatory process that can occur after a variety of infectious and noninfectious insults.The measurement of SIRS during the first day of hospitalization provided important information in assessing severity.[11] Parameters defining SIRS was recorded at the time of admission and those with persistent score were classified moderate or severe acute pancreatitis according to presence of organ damage whether transient or persistent and these patients were advised for further radiological investigation.

From a clinical point of view, the course of alcoholic and biliary acute pancreatitis is the same; however, because ERCP associated with endoscopic sphincterotomy can prevent further complications in patients with severe biliary pancreatitis, it is important to early recognize the biliary origin of the disease.[12]

Up to 30% of patients with acute pancreatitis are diagnosed of idiopathic acute pancreatitis after an initial evaluation including a complete clinical history, physical examination, analysis with calcium and triglycerides determination, and at least one transabdominal ultrasonography.Most common etiologies of AP are gallstone disease and alcohol consumption which accounts for almost 80 to 90% of the cases.Other etiologies include medicines, infections,metabolic disorders, trauma, ERCP etc.[13]Most of the patients in the study fell under biliary and alcoholic pancreatitis(85%).

It is clinically important because of the potential need for invasive treatment, such as endoscopic retrograde cholangiopan creatography.[14]In this study most of the cases were diagnosed clinically and with laboratory parameters combined and the etiology were tagged from radiological finding mostly by ultrasonography of abdomen or relevant history. A diagnosis of a biliary etiology in acute pancreatitis was supported by both laboratory and imaging investigations.In a large number of patients, with episodes of acute pancreatitis the etiology is not identified. even after initial clinical history, detailed physical examination, laboratory tests and biochemical tests and an transabdominal ultrasonography. This patient are considered with a unexplained acute pancreatitis. In these cases the treatment is restricted to improvement of symptoms. These patients after treated tend to have new episodes with the risk of raising the rates of morbidity and mortality. Therefore, the identification of a cause and its prompt treatment prevent recurrent episodes of pancreatitis.[15] EUS is able to identify significant pathology in patients in whom a diagnosis of 'idiopathic' pancreatitis has been made following standard investigations. Patients with untreated gallstones are at risk of recurrent attacks. Idiopathic pancreatitis should not be diagnosed unless EUS has been performed.[16]In my study,7 patients are labelled idiopathic,were these patients subjected to EUS cause could be identified.So those patients labelled idiopathic should undergo endoluminal ultrasonography in the post-acute-phase.Alexakis et al has also concluded it is the most sensitive method for the detection of cholelithiasis and choledocholithiasis and may reveal alternative aetiological factors such as a small ampullary or pancreatic cancer.A number of recent studies have shown that bile crystal analysis, a marker for microlithiasis, increases the yield of positive results over and above endoluminal ultrasonography, and should be considered as part of the modern investigative algorithm.[17]Unexplained pancreatitis represents a diagnostic challenge, although after different explorations a cause is found in the majority of these patients.[18]

The presence of microlithiasis or biliary sludge is an important cause of acute 'idiopathic' pancreatitis (upto 80% of patients). Microlithiasis and sludge can be detected by transabdominal/ endoscopic ultrasonography, ERCP or polarizing light microscopy of bile. Cholecystectomy is the treatment of choice, whereas endosc opic sphincterotomy and ursodeoxycholic acid maintenance therapy are effective alternatives. Sphincter of Oddi dysfunction can be identified as the cause of acute 'idiopathic' pancreatitis in up to 30% of patients. Manometry of Oddi's sphincter is the gold standard for its diagnosis.[19] Endoscopic sphincterotomy prevents recurrence in most patients. Anatomic abnormalities such as major papilla stenosis, pancreas divisum, pancreatic duct strictures and tumours may also cause acute 'idiopathic' pancreatitis.

Endoscopic sphincterotomy and surgery are effective treatments. Had those patients been undergone manometry of oddi's sphincter ,cause could be found.

Prospective and retrospective data were available from 200 consecutive patients with gallstone pancreatitis at a public teaching hospital from 2003 through 2007. Charts were examined for persisting CBD stones on ERCP and/or intraoperative cholangiography during laparoscopic cholecystectomy.In gallstone pancreatitis, serum total bilirubin level 4 mg/dL or greater on

hospital day 2 predicts persisting CBD stones with enough specificity to serve as a practical guideline for ERCP while minimizing unnecessary procedures.[20]As above,some have found raised serum bilirubin significantly correlated to biliary etology others did not found significance to etiology prediction.

Stimac et al concluded serum amylase, ALT, AST, alkaline phosphatase ($p < 0.001$), and urine amylase ($p < 0.01$) were significantly lower in patients with alcoholic pancreatitis while there were no differences in lipase, bilirubin, and gamma glutamyl transferase between patients with alcoholic pancreatitis and those with nonalcoholic pancreatitis.[21]In the study,serum bilirubin was higher in biliary group but not significant.

Pulmonary complications, including pulmonary edema and congestion, appeared to be the most significant factor contributing to death and occurred even in those cases where the pancreatic damage appeared to be only moderate in extent. Emphasis placed on the early recognition and treatment of pulmonary edema in all cases of moderate and severe AP should contribute significantly to an increase in survival in this disease.[22]Among the acute severe cases,one patient expired due to multiple organ failure.pulmonary complication was determing factor for death.

In patients with mild pancreatitis, surgery usually can be performed within 48 or 72 hours of admission or as soon as symptoms and amylase levels return to normal. For patients with severe disease, endoscopic sphincterotomy is emerging as the therapeutic modality of choice. Elective treatment of the associated biliary disease should be performed during the same hospitalization after the acute phase of the disease has subsided.[23] Pancreatitis remains a disease with a poor prognosis during the acute phase.[24]Mortality after admission has not declined since the 1970s. This presumably reflects the fact that no major innovations in the treatment of acute pancreatitis have been introduced.

Clinico biochemical evaluation is the key element in diagnosis and prediction of etiology and severity. Clinico-biochemical prediction for biliary cause of acute pancreatitis improves in the era of endoscopic ultrasonography with a higher sensitivity and overall accuracy. In centres where endoscopic ultrasonography is inaccessible or local expertise is unavailable, clinico-biochemical prediction of biliary cause of acute pancreatitis may provide a useful alternative in the initial management of this group of patients.[25]

CONCLUSION

Establishing a biliary etiology in acute pancreatitis is clinically important because of the potential need for invasive treatment.A simple and approximate prediction of biliary etiology of acute pancreatitis can be obtained from biochemical parameters especially from serum amylase.

LIMITATIONS OF THE STUDY

This study has some limitations. The sample size was not not big.The diagnosis of biliary cause was mostly made AUS and CECT(if done) and MRCP (if done). There were 7 patients of idiopathic pancreatitis, if they were subjected to further investigations like EUS or manometry of Oddi's sphincter , biliary cause could have been identified. This may be reason why difference in LFT could not reach significant level.Those who presented at different time from the onset of the disease process might have also altered the level of biochemical parameters.

Difference in timing of the collection of blood samples in which these analytes were measured and rapidity of changes in the biochemical markers of pancreatic and hepatobiliary damage in patients with pancreatitis due to biliary obstruction, serial measure might have reduced the discripancies.

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