A Study on Haematological and Coagulation Changes in Acute Pancreatitis – Prospective Study

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ABSTRACT

Introduction: Acute pancreatitis (AP), a common cause of acute abdominal pain, is usually a mild, self-limited disease. However, some 20-30% of patients develop a severe disease manifested by pancreatic necrosis, abscesses or pseudocysts, and extrapancreatic complications, such as vital organ failure. Study aimed to observe the Haematological and coagulation changes prospectively in patients with acute pancreatitis and to correlate the changes to its severity.

Material and Methods: Detailed clinical history of all 50 patients and a thorough physical examination of all 50 patients have been done. Serum amylase/Lipase was done for all patients. Liver function tests, Renal function tests, X-ray chest PA view, Ultra sonogram abdomen, and contrast-enhanced CT abdomen were done for all patients to rule out various complications associated with acute pancreatitis.

Results: Fibrinogen levels were lower in 16% of the study group, of which 87.5% was in severe pancreatitis group. These patients were in severe DIC. High fibrinogen values were seen in 38%, of which severe pancreatitis accounts to 57.9%. These patients were in the early stage of the disease. In contrast, FDP levels were found to be higher in 16% of the study group, and all of them belong to the severe group. The fibrinogen and FDP values are therefore significantly influenced by inflammatory cytokines with variable thrombohaemorrhagic manifestations.

Conclusion: Haematological and coagulation abnormalities were more common in severe acute pancreatitis. Though full Blown DIC seen in few patients, cases with impending DIC and cases with the high potential to develop DIC can be recognized early and can be managed effectively.

Keywords: Prothrombin time, Thromboplastin, Platelets, Fibrinogen.

INTRODUCTION

Acute pancreatitis was defined in the Atlanta symposium as an acute inflammatory process involving the pancreas that further involve peripancreatic tissues and organs remote from the pancreas. Criteria had been defined for severity which include organ failure (Pulmonary insufficiency, shock and renal failure) and /or complications involving locally which include pseudocyst. pancreatic necrosis and pancreatic abscess.[1]

Acute Pancreatitis produces a severe inflammatory response which is mainly responsible for acinar cell damage which leads to release of inflammatory mediators like cytokines, TNF and PAF thereby resulting in a systemic inflammatory response.[2]

These inflammatory mediators alter the normal hemostatic mechanism by acting in Paracrine or autocrine loops to activate the monocytes, neutrophils to site of injury and these activated cells in turn expresses the tissue factor in the injured pancreatic cell and alter the coagulation pathway.[3]

The Hypothesis states that these coagulation changes may be due to early consumption of coagulation factors which are secondary to enzymes of pancreas, especially trypsin, or it may be secondary to vascular injury.[4]

Hence recognition of these haematological and coagulation disturbance at earliest is essential especially disseminated intravascular coagulation to improve the outcome in patients with acute pancreatitis.

Study aimed to observe the Haematological and coagulation changes in patients with acute pancreatitis and correlating the changes to its severity.

MATERIAL AND METHODS

Study was done in the Department of Medical and surgical Gastroenterology of tertiary care center. Patients who were admitted in Department of Medical and surgical Gastroenterology and those patients admitted in other Medical and surgical wards with History and investigations suggestive of Acute pancreatitis were included in the study.

Exclusion Criteria

- Patients not willing for study.
- Patients with known Haematological disorders.
- Patients with pre-existing or coexisting Chronic liver disease
- Pregnancy/Postpartum
- H/o surgery in recent past
- Post ERCP pancreatitis

50 patients with clinical features of abdominal pain characteristic of acute pancreatitis, serum amylase and /or lipase≥3times upper limit of normal and CT scan showing characteristic features of acute pancreatitis were chosen and their Haematological and coagulation indices were studied

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How to cite this article: A. Shafique, T. Usha. A study on haematological and coagulation changes in acute pancreatitis – prospective study. International Journal of Contemporary Medical Research 2018;5(11):K1-K5.

DOI: http://dx.doi.org/10.21276/ijcmr.2018.5.11.23

prospectively over a period of 1 year. Detailed clinical history of all 50 patients and thorough physical examination of all 50 patients have been done. Serum amylase/Lipase was done for all patients. Liver function tests, Renal function tests, X-ray chest PA view, Ultra sonogram abdomen and contrast enhanced CT abdomen were done for all patients to rule out various complications associated with acute pancreatitis. Etiological workup was done for all 50 patients with relevant investigations. Patients were grouped into mild and severe pancreatitis by using Balthazar CT scoring system and Modified CT severity index score.

RESULTS

88% of acute pancreatitis patients were males when compared to 12% in females. 42% of acute pancreatitis in the 31-40 age group and 28% in the 21-30 group. Rest of age group form just 30% in this study population. Majority of patients were alcoholic (60%) in this study followed by idiopathic group (24%) and gallstones (12%). 64%% of study subjects were in the severe group and 36% in the mild group of acute pancreatitis. Anaemia found in 78% of acute pancreatitis patients. Leukocytosis was seen in 20% of study subjects and leucopoenia found only in 4%. Polymorph levels were higher in 28% of the study population. Haematocrit levels were lower in 76% of patients, where higher Haematocrit values seen only in 6%. Low platelets were found in 34% and high platelets observed in 6%. INR levels were higher in 28% of study subjects. Increase in APTT levels in 24% of the study population. Increase in fibrinogen levels in 38% and a decrease in fibrinogen levels by 16%. Increase in FDP levels in 16% of study subjects.

Out of 50 study subjects, 32(78%) were anaemic in this

INR		Grade		Total	P value
		Mild	Severe		
<1.2	Count	13	23	36	0.979
	% within INR	36.1%	63.9%	100.0%	
	% within Grade	72.2%	71.9%	72.0%	
>1.2	Count	5	9	14	
	% within INR	35.7%	64.3%	100.0%	
	% within Grade	27.8%	28.1%	28.0%	
Total	Count	18	32	50	
	% within INR	36.0%	64.0%	100.0%	
	% within Grade	100.0%	100.0%	100.0%	

Table-1: INR variation in relation to grade of acute pancreatitis:

INR		Grade		Total	P value
		Mild	Severe		
Normal	Count	16	22	38	0.109
	% within APTT	42.1%	57.9%	100.0%	
	% within Grade	88.9%	68.8%	76.0%	
High	Count	2	10	12	
	% within APTT	16.7%	83.3%	100.0%	
	% within Grade	11.1%	31.3%	24.0%	
Total	Count	18	32	50	
	% within APTT	36.0%	64.0%	100.0%	
	% within Grade	100.0%	100.0%	100.0%	

Table-2: APTT variation in relation to grade of acute pancreatitis

Fibrinogen		Grade		Total	P value
		Mild	Severe		
Normal	Count	9	14	23	Chi Square 0.313
	% within Fibrinogen	39.1%	60.9%	100.0%	
	% within Grade	50.0%	43.8%	46.0%	
Low	Count	1	7	8	
	% within Fibrinogen	12.5%	87.5%	100.0%	
	% within Grade	5.6%	21.9%	16.0%	
High	Count	8	11	19	
	% within Fibrinogen	42.1%	57.9%	100.0%	
	% within Grade	44.4%	34.4%	38.0%	
Total	Count	18	32	50	
	% within Fibrinogen	36.0%	64.0%	100.0%	
	% within Grade	100.0%	100.0%	100.0%	

Table-3: Fibrinogen variation in relation to grade of acute pancreatitis

FDP		Grade		Total	P value
		Mild	Severe		
Normal	Count	18	24	42	0.021
	% within FDP	42.9%	57.1%	100.0%	
	% within Grade	100.0%	75.0%	84.0%	
High	Count	0	8	8	
	% within FDP	.0%	100.0%	100.0%	
	% within Grade	.0%	25.0%	16.0%	
Total	Count	18	32	50	
	% within FDP	36.0%	64.0%	100.0%	
	% within Grade	100.0%	100.0%	100.0%	

Table-4: FDP variation in relation to grade of acute pancreatitis

APTT		Fibrinogen			Total	P value
		Normal	Low	High		
Normal	Count	20	4	14	38	0.104
	% within APTT	52.6%	10.5%	36.8%	100.0%	
	% within Fibrinogen	87.0%	50.0%	73.7%	76.0%	
High	Count	3	4	5	12	
	% within APTT	25.0%	33.3%	41.7%	100.0%	
	% within Fibrinogen	13.0%	50.0%	26.3%	24.0%	
Total	Count	23	8	19	50	
	% within APTT	46.0%	16.0%	38.0%	100.0%	
	% within Fibrinogen	100.0%	100.0%	100.0%	100.0%	

Table-5: Cross tabular variation between APTT and fibrinogen

APTT		FDP		Total	P value
		Normal	High		
Normal	Count	33	5	38	0.329
	% within APTT	86.8%	13.2%	100.0%	
	% within FDP	78.6%	62.5%	76.0%	
High	Count	9	3	12	
	% within APTT	75.0%	25.0%	100.0%	
	% within FDP	21.4%	37.5%	24.0%	
Total	Count	42	8	50	
	% within APTT	84.0%	16.0%	100.0%	
	% within FDP	100.0%	100.0%	100.0%	

Table-6: Cross tabular variation between APTT and FDP

FDP		Fibrinogen			Total	P value
		Normal	Low	High		
Normal	Count	21	6	15	42	0.416
	% within FDP	50.0%	14.3%	35.7%	100.0%	
	% within Fibrinogen	91.3%	75.0%	78.9%	84.0%	
High	Count	2	2	4	8	
	% within FDP	25.0%	25.0%	50.0%	100.0%	
	% within Fibrinogen	8.7%	25.0%	21.1%	16.0%	
Total	Count	23	8	19	50	
	% within FDP	46.0%	16.0%	38.0%	100.0%	
	% within Fibrinogen	100.0%	100.0%	100.0%	100.0%	

Table-7: Cross tabular variation between FDP and fibrinogen

study. But when these anaemic patients were compared with the grade of pancreatitis, 64.1% were in the severe group and 35.9% in the mild group the difference was not statistically significant (P>.05).

Only 10 (20%) of study subjects have leukocytosis in this study. Leukocytosis was found in 80% of severe type when compared with 20% of the mild type. But the percentage within the grade is 25% in the severe group and 11.1% in mild group. Hence the difference was not statistically significant. Increase in Polymorphs seen more in severe acute pancreatitis (64.3%) than in mild acute pancreatitis (35.7%). But Polymorphs percentage within the grade is 28.1% in severe

acute pancreatitis and 27.8% in mild acute pancreatitis. Hence the difference was not statistically significant. (P>0.05).

Haemoconcentration (HCT>45%) which is a predictor of severe pancreatitis was seen only in 6%. Majority of the study subjects had decreased haematocrit values (76%). The difference was not statistically significant when the haematocrit values are compared with the grade of pancreatitis. (P>0.05).

Thrombocytopenia was observed in 17 study subjects (34%) in this study. In these 17 patients, 12 (70.6%) were in the severe group and 5 (29.4%) in mild group. But the percentage of thrombocytopenia within the grade was 37.5% in the severe group, and 27.8% in the mild group and hence the differences were not statistically significant (P>0.05).

14 (28%) study subjects showed increase in INR values in this study. In this 14 study subjects 9 (64.3%) were in severe group and 5(35.7%) in mild group. But percentage of increase INR within grade was 28.1% in severe category and 27.8% in mild category and hence the difference was not statistically significant (P>0.05) (table-1).

12 (24%) of study subjects have high APTT value and the value was more in severe pancreatitis group (83.3%) than in mild group (16.7%). But the percentage within the grade was 31.3% in severe group and 11.1% in mild group and the difference was not statistically significant. (P>0.05) (table-2).

Out of 50 patients low fibrinogen observed in 8 (16%) and high fibrinogen observed in 19 (38%) clients. Majority of low fibrinogenemia belonged to severe category (87.5%). Increase in fibrinogen levels were observed in 11 (57.9%) patients in severe category and 8 (42.1%) patients in mild category. The percentage difference between the above variables within grade was not statistically significant (P>0.05) (table-3).

High level of FDP were observed in 8 (16%) patients and all 8 cases were observed in severe category. Hence the difference between 2 grades were statistically significant (P<.05) (table-4).

This table 5 showed that 4 patients (33.3% within APTT) had rise in APTT value and decrease in fibrinogen. These patients can be considered as full blown DIC. 4 patients (50% within fibrinogen) have decrease in fibrinogen values but normal APTT values. These patients were early in development of DIC. The difference between 2 variables were not statistically significant (P>0.05).

Patients (25%within APTT) had both High APTT value and High FDP values indicative of DIC in these patients. 5 patients (62.5%within FDP) had High FDP values but normal APTT values, indicating that these patients were in early severe pancreatitis and feature suggestive of impending DIC. The difference between these two variables were not statistically significant (P>0.05) (table-6).

2 patients (25%within FDP) had low fibrinogen levels and High FDP levels indicative of full blown DIC. 6 patients (75% within fibrinogen) have low fibrinogen values but a normal FDP value implies these patients were in impending DIC. The difference between these 2 variables were not statistically significant (P>0.05) (table-7).

DISCUSSION

In this study, patients were graded in to mild and severe pancreatitis by Balthazar CT grade system/CTSI scoring system.[5] After satisfying the inclusion and exclusion criteria, Haematological and coagulation changes were assessed in reference to these 2 grades.

Literature research showed that haematological abnormalities in acute pancreatitis were recorded in a prospective study by Desmond Murphy and Clement Imrie.[1]

In another study by Li-Pe cheng[6], he studied the influence of coagulation function on acute pancreatitis on 56 patients of acute pancreatitis with normal control group and found that the coagulation parameters were significantly increased indicating bad prognosis though the difference between the 2 groups were not statistically significant. In our study we found similar coagulation changes.

Haemoconcentration (HCT>45%) is a sign of severe acute pancreatitis.[3] However this was found only in 6% of our study group, where as decrease in haematocrit value were noted in 76%. The decrease in haematocrit is due to the fact majority of patients in study group were anaemic. The Patients in our study group had haemoglobin level ranging from 6-12gms%.However the corresponding haematocrit was appreciably higher in most of the patients in severe acute pancreatitis indicating haemoconcentration.

Leukocytosis was noted in 20% of study group and they are found more (80%) in severe acute pancreatitis. Although neutrophilic dominance is noted in 28 out of 32 patients with severe acute pancreatitis.4 had significant lymphocytosis affecting the P value. This is probably due to subclinical viral infection.[5] Though these variables were more in severe pancreatitis, the difference between these variables between mild and severe group were not statistically significant (P>0.05).

Thrombocytopenia was noted in 34% of study group, of which 70.6% were belong to severe acute pancreatitis. Thrombocytopenia could be due to a) a part of DIC with associated global prolongation of coagulation parameters or b) manifestation of thrombotic microangiopathy resulting from diffuse endothelial injury and platelet activation.[8]

Prothrombin time was found to be increased in 28% of patients and was seen more in severe acute pancreatitis group (64.3%). Similarly increase in APTT values were seen in 24%,of which 83.3% were in severe pancreatitis group.

Fibrinogen levels were lower in 16% of study group, of which 87.5% was in severe pancreatitis group. These patients were in severe DIC. High fibrinogen values were seen in 38%, of which severe pancreatitis accounts to 57.9%.These patients were in early stage of the disease and did not have frank haemostatic disturbance. This increased fibrinogen value in 38% of patients can be explained by the fact that fibrinogen is a acute phase reactant like CRP, and hence can be increased with severe inflammation.[9] Though these variables were more in severe pancreatitis, the difference between these variables between mild and severe group were

not statistically significant (P>0.05).

In contrast FDP levels were found to be higher in 16% of study group and all of them belong to severe group of pancreatitis. Hence the difference between these variables between mild and severe group were statistically significant (P<0.05%).

Cross tabulation done between APTT and fibrinogen values showed that 4 patients (33.3% within APTT) had rise in APTT value with decrease in fibrinogen values. These parameters could indicate DIC in these patients. 4 patients (50% within fibrinogen) have decrease in fibrinogen values but normal APTT values. These patients can be early in development of DIC and these patients should receive more attention for better clinical outcome.

Similarly when cross tabulation was done between APTT and FDP, 3 patients(25%within APTT) have increased values of both APTT and FDP indicating DIC whereas 5 patients(62.5%within FDP) with high FDP value had normal APTT values. When fibrinogen and FDP was cross tabulated, 2 patients (25%within FDP) have features of full blown DIC with decrease in fibrinogen value and increase in FDP values. 6 patients (75% within fibrinogen) have low fibrinogen values but with normal FDP values. Out of these 6 patients 5 were in severe category. It has been observed that the fibrinogen levels vary significantly in the first week of acute severe pancreatitis. Fibrinogen synthesis and lysis go hands together in acute pancreatitis depending on the inflammatory response. The natural anticoagulants (protein-C,AT-111) are also variably up-regulated and down-regulated by the acute phase reactants, essentially working against thrombosis.[10] The fibrinogen and FDP values are therefore significantly influenced by inflammatory cytokines with variable thrombohaemorrhagic manifestations[5]

Though these cross tabulation variables with APTT, fibrinogen and FDP give clue about DIC and impending DIC developing in these patients, the difference between these variables between mild and severe group were not statistically significant(P>0.05).

CONCLUSION

Haematological and coagulation abnormalities were more common in severe acute pancreatitis. Though evidence of full blown Disseminated Intravascular Coagulation is seen in few patients, the cases which were impending Disseminated Intravascular Coagulation and cases which have high potential to develop Disseminated Intravascular Coagulation were recognized and could be managed effectively. The difference between variables comparing haematological and coagulation indices with severity of pancreatitis were not statistically significant except for the increase in FDP value which was statistically significant. Therapeutic regimens like Activated protein C, Anti-thrombin 111, Platelet activating factor modulating agents, Factor V11a inhibitors could be tried in near future to improve the clinical outcome of patients with severe coagulatory disturbance in acute pancreatitis.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 15-10-2018; **Accepted:** 02-11-2018; **Published:** 22-11-2018