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Study of Serum Enzymes in Organophosphorus Poisoning in a Tertiary Care Hospital in South India

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ABSTRACT

Organophosphorus poisoning is one of the important causes of mortality and morbidity in agricultural countries like India. Measuring Serum Cholinesterase is commonly used for diagnosis of Organophosphorus poisoning as its levels decreases in poisoning. But, because of wide inter-individual variability and less availability, easily available and more reliable biochemical parameters are needed for both diagnosis and prognosis. The aim of this study is to estimate various enzymes on the day of admission for correlation with severity of Organophosphorus poisoning in South Indian population. 70 patients of OP poisoning in a tertiary care centre in Tamil Nadu were taken up for the study and their clinical severity characterized according to Peradeniya Organophosphorus poisoning (POP) scale. Serum levels of Acetylcholinesterase, Creatine Kinase (CK), Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Amylase, Lactate Dehydrogenase (LDH), were measured at the day of admission. Serum Acetylcholinesterase, Serum CK, Amylase, LDH were all elevated and correlated well with the severity while AST and ALT showed no changes. Thus, from this study we conclude that the assessment of serum enzymes like LDH, Amylase, CK are very useful biochemical markers that reflect the severity of OP poisoning and help to identify the occurrence of the complications early so that the mortality can be reduced.

Keywords: Organophosphorus poisoning, POP scale, Serum Enzymes.

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INTRODUCTION

Organophosphorus (OP) poisoning is a global health problem. Widespread use, easy access and low cost have been gradually increasing the incidence of OP poisoning in India.

Organophosphorus compounds (OPC) are a diverse group of insecticides They can be efficiently absorbed by inhalation,ingestion,and skin penetration. On absorption, they act by inhibiting the enzyme Acetylcholinesterase (AChE). This results in accumulation of Acetylcholine (Ach) at synapses and myoneural junction leading to cholinergic overactivity[1].

Respiratory, neurological, and cardiac complications are the common causes of morbidity and mortality in these patients[2]. Early recognition and prompt ventilator support may improve survival. Both clinical assessment and laboratory investigations are very important for diagnosis and early recognition of complications.

Peradeniya Organophosphorus Poisoning (POP) scale is one of the clinical grading systems used to assess severity of OP poisoning. The scoring system classifies OP poisoning into mild, moderate and severe based on five important clinical manifestations namely pupillary constriction, fasciculations, heart rate, respiratory rate and level of consciousness.

A low level of serum Pseudocholinesterase (CHE)/Butrylcholinesterse is used for the diagnosis of organophosphorus (OP) poisoning. But, it is not available in all centers and it is subject to a number of interindividual variations. Thereby, there is a need for an easily available biochemical parameter to assess the severity and for early identification of complications. A number of studies have been carried out to find out the usefulness of biochemical parameters like serum amylase, serum creatine kinase (CK), serum lactate dehydrogenase (LDH) in assessing the severity and prognosis of OP poisoning.

In OP poisoning, raised serum amylase is common due to pancreatic injury, cholinergic stimulation of pancreatic secretions and obstruction at the sphincter of Oddi level[3]. Elevations are seen in serum LDH and CK levels as a result of muscle injury[4].

Organophosphorus compounds are said to cause hepatotoxicity since liver is the main site of their oxidative metabolism.

Aim And Objectives

Aim

To assess the severity in OP poisoning using biochemical parameters like Serum Cholinesterase, Serum Amylase, Serum Creatine kinase, Serum Lactate Dehydrogenase, Serum Alanine Transaminase (ALT), Serum Aspartate Transaminase (AST), Serum Alkaline Phosphatase (ALP) in a Tertiary Care Centre in South India.

Objectives

- To estimate the serum levels of ALT, AST, ALP, Cholinesterase, Amylase, Creatine kinase,Lactate dehydrogenase in OP poisoning
- To correlate the serum levels of ALT, AST, ALP, Cholinesterase, Amylase, Creatine kinase, Lactate dehydrogenase, with clinical severity as assessed by POP scale in OP poisoning

MATERIALS AND METHODS

This was a prospective, observational study conducted in Tirunelveli Medical College Hospital, Tirunelveli after getting approval from the institutional ethical committee.

70 patients admitted in the Tirunelveli Medical College hospital with acute OP poisoning was taken for the study considering the inclusion and exclusion criteria. Informed written consent was obtained from all the patients.

Inclusion Criteria

Patients admitted in Tirunelveli Medical College Hospital with history of consumption of Organophosphorus compounds, characteristic clinical manifestations and physical evidence of poison consumed

Exclusion Criteria

1. Patients who have consumed other poisons along with OP poison
2. Patients with history of alcohol intake with the poison
3. Patients with known history of Chronic Lung Disease, Pancreas, and Musculoskeletal disorders
4. Patients with chronic history of Smoking, Alcoholism.

The clinical severity of the patients was assessed using the POP scale on the day of admission. After obtaining consent, 3ml of venous blood was collected from each subject and transferred to serum separator tube and allowed to clot for 30 minutes and centrifuged at 1000 x g for 15 minutes for clear separation of serum. Immediately after the serum was separated, the following parameters were estimated.

1. Serum Amylase
2. Serum Creatine kinase
3. Serum Lactate dehydrogenase
4. Serum Butrylcholinesterase
5. Serum AST
6. Serum ALT
7. Serum ALP

Table 1: Peradeniya Organophosphorus Poisoning (POP) scale

Parameter	Criteria	Score
Pupil size	≥2 mm	0
	<2 mm	1
	pinpoint	2
Respiratory rate	<20/min	0
	≥20/min	1
	≥20/min with central cyanosis	2
Heart rate	>60/min	0
	41-60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized/ continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal command	1
	No response to verbal command	2
Seizures	Absent	0
	present	1
0-3: mild poisoning, 4-7: moderate poisoning, 8-11: severe poisoning		

Statistical Analysis

SPSS (Statistical Package for Social Science) version 16.0 software was used for analysing statistical

data. Various biochemical data are presented as mean and standard deviation. Continuous data were compared by independent student t tests. One way ANOVA tests was used to compare more than 2 groups. Categorical data were compared by Pearson chi-square test. Significance was defined by ' p' values less than 0.05 using a two-tailed test. Pearson Correlation was used to find the correlation between the various analytes with the POP score.

RESULTS

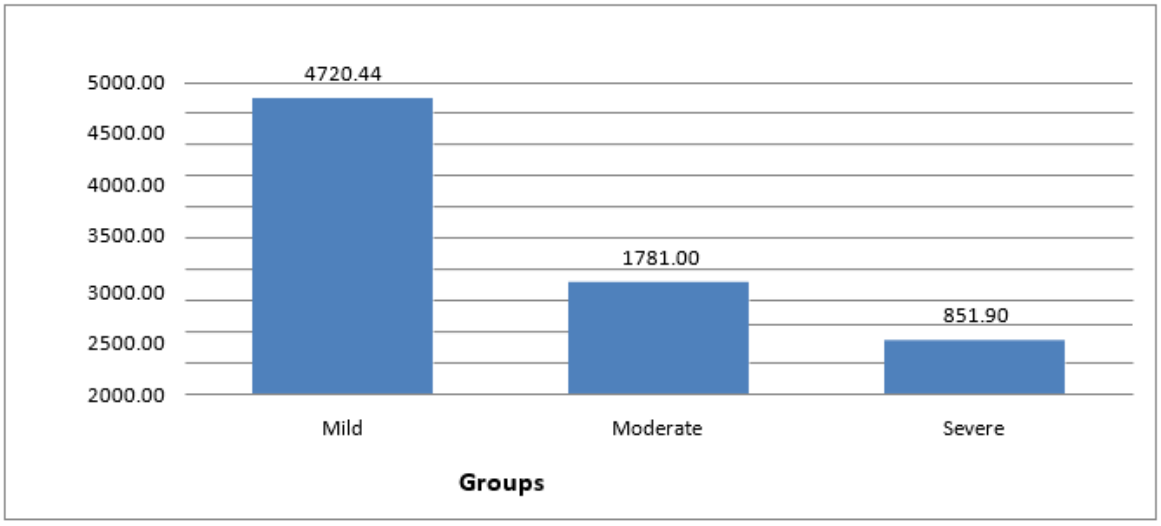
The mean serum Cholinesterase level was 2698.07 U/L which is much lower than the reference value. This is in accordance with the studies done by Eddeleston et al and Nouira et al[6,7,8]. This is attributed to the fact that OP compounds exert their toxicity by inhibiting cholinesterase enzyme, both true and plasma cholinesterase Likewise, there was also a significant correlation in the mean serum cholinesterase level between the three groups – mild (4720.44 U/L), moderate (1781 U/L), severe (851.9 U/L) with a 'p' value of < 0.01. This suggests that the serum cholinesterase levels reflect the clinical severity of OP poisoning. Similar results were observed in a study by Panda et al , where cholinesterase activity with severity of poisoning [5]. But assessment of clinical severity based on the activity of the cholinesterase alone remains controversial. This is because some studies using serial estimations of serum Cholinesterase activity have found that the correlation with clinical severity was seen only during the early stages of poisoning [7,9]. In the later stages the enzyme levels did not show any correlation with severity of poisoning. It is also seen that patients who had very low cholinesterase activity had very poor prognosis and high mortality rates. But it can be used as a sensitive marker to detect exposure to organophosphorous compounds[7]. Furthermore, serial assays can also be used to monitor effectiveness of the therapy since recovery of enzyme activity denotes fall in toxin level.

It should be evaluated carefully because the enzyme activity is subject to a large number of interindividual variations and its non -specific nature. A genetically determined low baseline activity of plasma pseudocholinesterase is found in around 3% of individuals. Various studies have shown that low serum cholinesterase activity is seen in Liver disease, Heart disease, Malignant Neoplasms, Malnutrition, Chronic Alcoholism, Dermatomyositis and Pregnancy[6,7,8]. Cocaine, Carbon disulfide, Benzalkonium salts, and Organic mercury compounds are some of the toxins inhibiting plasma pseudocholinesterase activity.

Table 2: Association of serum Cholinesterase with severity as assessed by POP Score.

		N	Mean	Std. Deviation	'p' value
Serum Cholinesterase (IU/L)	Mild	25	4720.44	1487.25	<0.0001
	Moderate	35	1781.00	1021.61	
	Severe	10	851.90	179.23	
	Total	70	2698.07	1921.01	

Figure 1: Bar diagram showing association of Serum Cholinesterase with severity as assessed by POP Score



Measuring the RBC AChE activity is considered more reliable than measuring PChE[7,8] because it is said to be more specific than BchE. Even though AchE activity is said to correlate well with the severity, most laboratories do not have this facility especially in developing countries. Furthermore, certain pesticides inhibit Butyrylcholinesterase more effectively than they inhibit Acetylcholinesterase[8]. BChE activity is also more efficient in monitoring response to therapy because it falls before AChE and recovers within weeks, much faster than AChE. This is because AchE regeneration rate depends on erythropoiesis and thus is slower at less than 1% per day. It may take 1-3 months for complete recovery[8]. Though AChE is considered more specific than BchE, it is also subject to a number of intra-assay and interindividual variations. It is reduced in conditions such as Leukemia, Multiple Myeloma, and Newborn[6,8]. It is also elevated whenever there is increased erythropoiesis like certain hemolytic anemias.

In the present study, the mean AST (27.56 U/L), ALT (21.30 U/L), ALP (90.23 U/L) levels were well within the normal reference range. There was no significant correlation with the clinical severity. This is consistent with the study done by AB Patel et al who said that even though OPC poisoning causes hepatic damage its clinical significance is doubtful[10]. Mitochondrial injury, free radical induced oxidative damage, metabolic alterations are some of the proposed mechanisms behind OP induced hepatotoxicity. But it is said that the damage is not severe enough to raise the liver enzymes. Moreover, main limitation of liver function test in assessing the clinical severity in OP poisoning is that any underlying silent chronic liver disease has to be ruled out.

Table 3: Association of Liver enzymes with severity assessed by POP Score

		N	Mean	Std. Deviation	'p' value
Serum SGOT(U/L)	Mild	25	29.44	13.36	0.594
	Moderate	35	26.29	11.69	
	Severe	10	27.30	6.60	
	Total	70	27.56	11.71	
Serum SGPT(U/L)	Mild	25	20.72	9.61	0.525
	Moderate	35	20.69	11.49	
	Severe	10	24.90	11.01	
	Total	70	21.30	10.73	

The mean serum Amylase levels in the groups were mild (52.32 U/L), moderate (102.29 U/L), severe (157.20 U/L). The total mean level was 92.29 U/L which was higher than the reference range. The correlation with the POP score was significant with 'p' value <0.01. this clearly shows that the serum amylase levels are elevated in OP poisoning and it correlates with the clinical severity. This is similar to other studies done by Amenvermez R and Lee WC[3,11]. Pancreatic ductal hypertension and cholinergic stimulation leading to increased exocrine, pancreatic secretion are said to be the main causes[12,13,14,15]. Though OP induced acute pancreatitis can also cause raised amylase levels, it is quite rare. OP induced parenchymal injury, free radical mediated damage, duct obstruction are said to be the main cause for pancreatitis. This can be ruled out by further imaging studies and estimation of serum Lipase[12.13]. Serum lipase levels are elevated only in those patients who develop OP induced pancreatitis.

Table 4: Association of Serum Enzymes with severity assessed by POP Score

		N	Mean	Std. Deviation	'p' value
Serum ALP(U/L)	Mild	25	86.44	18.54	0.623
	Moderate	35	93.86	38.88	
	Severe	10	87.00	24.00	
	Total	70	90.23	30.87	
Serum Amylase(U/L)	Mild	25	52.32	20.65	<0.0001
	Moderate	35	102.29	46.70	
	Severe	10	157.20	68.64	

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	Total	70	92.29	55.48	
Serum LDH(U/L)	Mild	25	418.28	155.35	0.328
	Moderate	35	466.43	139.02	
	Severe	10	492.60	183.72	
	Total	70	452.97	151.91	
Serum CK(U/L)	Mild	25	699.24	407.69	0.733
	Moderate	35	701.51	283.32	
	Severe	10	610.90	278.80	
	Total	70	687.76	329.40	

Figure 2: Bar diagram showing Association between Serum Amylase and severity assessed by POP Score

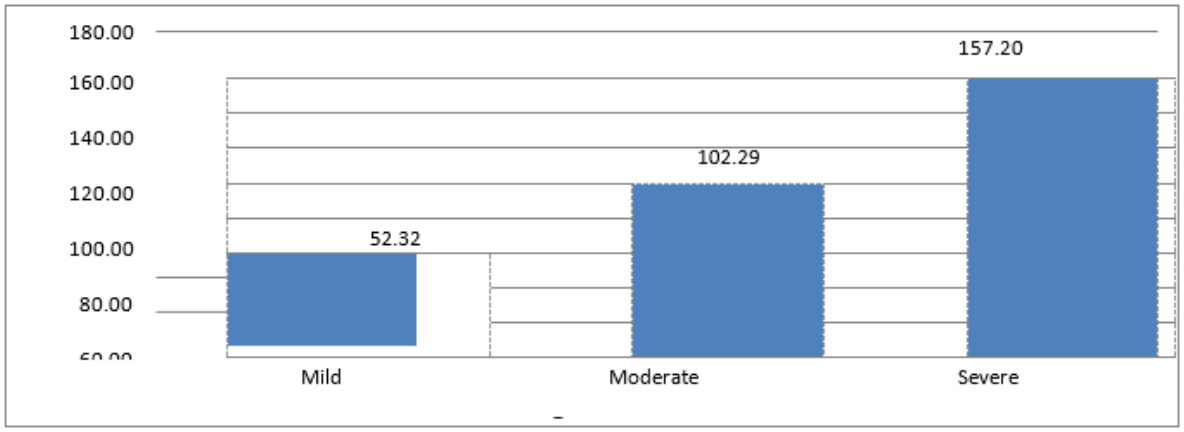
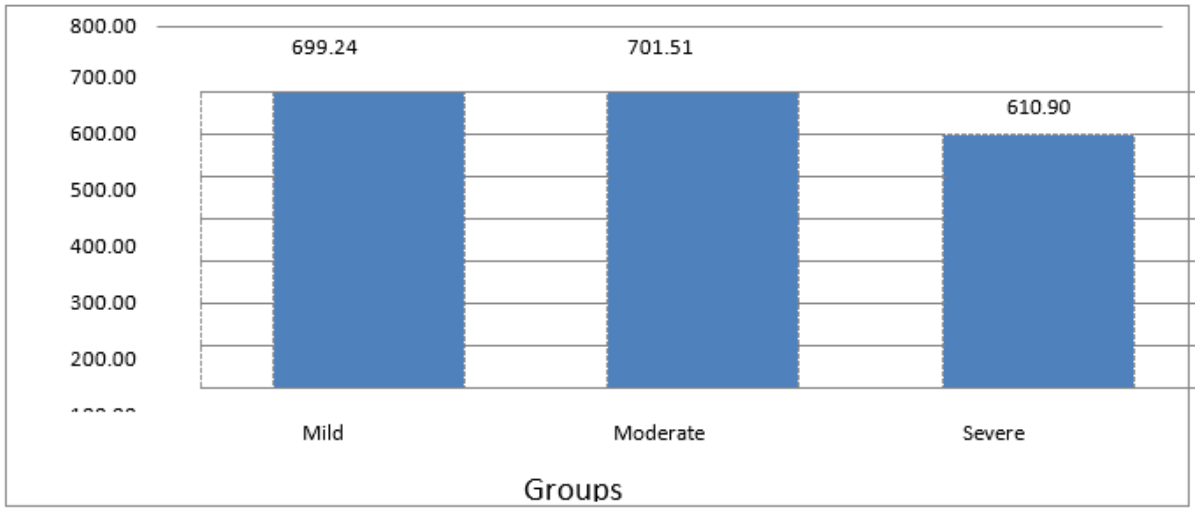


Figure 3: Bar diagram showing association between Serum CK and severity assessed by POP Score



The mean CPK level in our study is 687.76 U/L which is much higher than the normal reference population. Karalliedde et al and Henry et al said this may be due to the muscle injury induced by cholinergic crisis of OPC poisoning and. OP -induced myopathy[16]. Elevated serum CPK level is considered as most sensitive indicator of muscle injury and to reflect the magnitude of acute muscle necrosis[16]. In our study, the levels did not correlate with the clinical severity- mild (701.51 U/L), moderate (701.51 U/L) and severe (610.90 U/L) and 'p' value of 0.733. This is in accordance with a study done by Bleecker et al who showed that raised CPK and muscle injury does not mean progression to intermediate

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syndrome and respiratory failure[17]. The main pathogenesis of intermediate syndrome seem to be neuromuscular junction transmission impairment rather than muscle injury[18,19,20]. This is in contrast with John et al. who reported that the presence elevated CPK at the time of admission may predict the subsequent occurrence of intermediate syndrome in organophosphate poisoning[20] . More studies using a large population cohort, long term follow up and serial measurements is needed to assess the usefulness of serum CPK as a prognostic marker and in predicting intermediate syndrome.

Figure 4: Bar diagram showing Association between Serum LDH and Severity assessed by POP Score

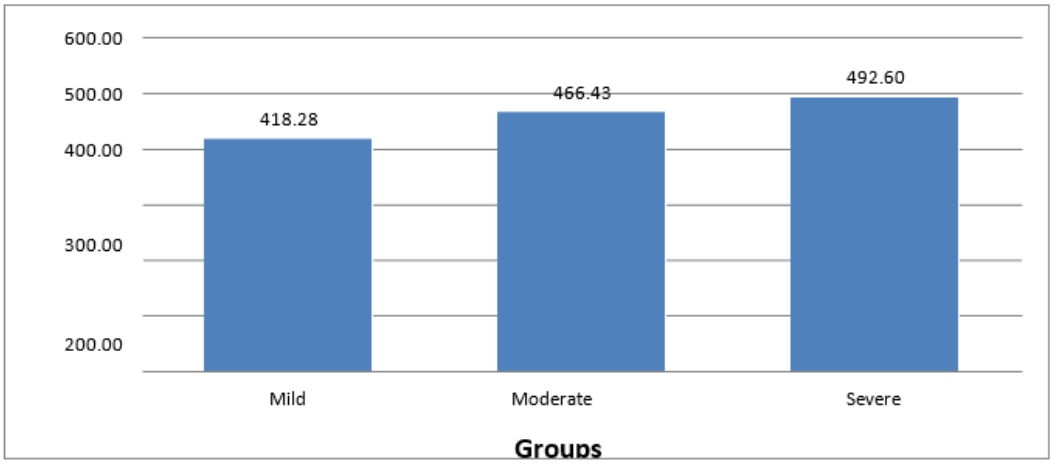

Table 5: Correlation of selected parameters with POP Score

		Sugar (mg/dl)	WB C	Cholinesterase (IU/L)	Amylase (U/L)	LDH (U/L)	CK (U/L)
POP score	Pearson Correlation n	.282*	.470**	-.775**	.651**	.104	-.019
	'p' value	.018	.000	.000	.000	.393	.873
	N	70	70	70	70	70	70

In this study, the mean serum LDH level was found to be 452.97 U/L which is higher than the reference range. This is in agreement with a study done by Panda et al and it is said to be due to the muscle injury and the anaerobic glycolysis seen in the poisoning[5,11]. Even though there was a difference between the three groups, it was not statistically significant with a 'p' value of 0. 328.Panda et al suggested that serial estimations may be more useful in assessing the severity[5].

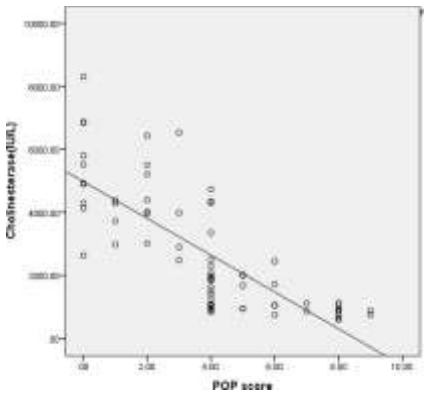

Figure 5: Correlation between Serum Cholinesterase and POP Score

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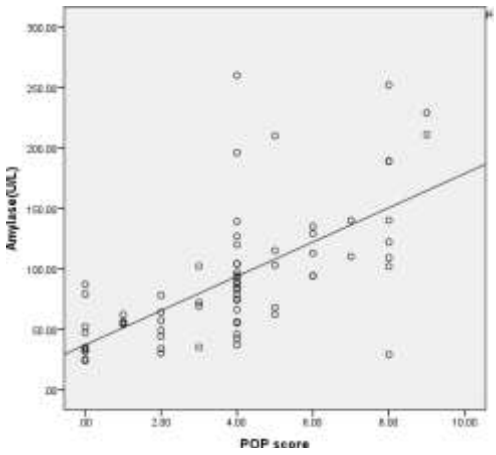

Figure 6: Correlation between Serum Amylase and POP Score

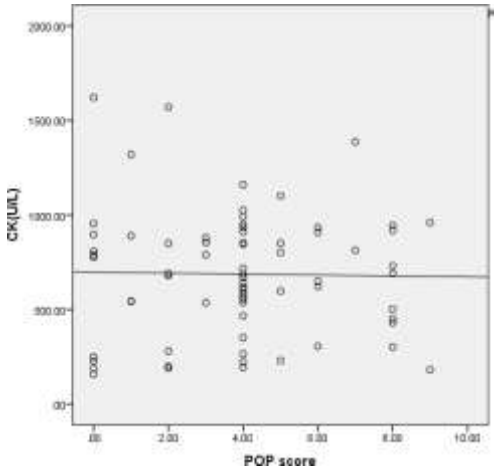

Figure 7: Correlation between Serum CK and POP Score

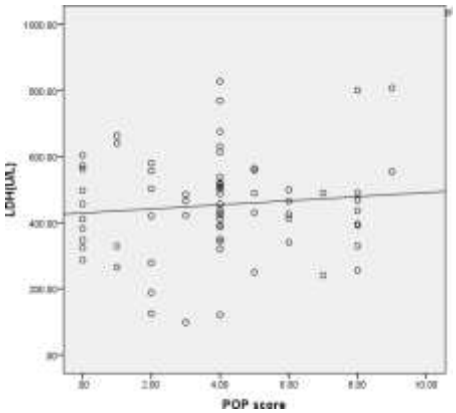

Figure 8: Correlation between Serum LDH and POP Score

CONCLUSION

Among the biochemical investigations, Serum cholinesterase was elevated and had a significant correlation with the POP score and severity. Serial estimations may be more reliable. Its main disadvantage is that it is not available in all the hospitals and is also elevated in many other conditions.

- Serum Amylase was elevated and showed significant correlation with the POP score and clinical severity.

- Serum LDH was elevated reflecting the muscle injury. It also showed correlation with the clinical severity but it was not statistically significant. Significant difference was not found between the moderate and severe groups

- Serum CK was higher than the reference range due to the muscle damage in cholinergic crisis. But there was no significant correlation with the severity.

- Serum AST, ALT, ALP were within the normal reference interval and did not show any significant change in OPC patients

The incidence of OP poisoning continues to rise in developing countries like India due to the easy availability of pesticides. It is an acute emergency with a high degree of morbidity and mortality. Early identification of complications and adequate treatment can reduce the case fatality rate. The above study shows that various biochemical parameters are altered in OP poisoning reflecting the underlying pathogenesis. Serum Cholinesterase and Amylase levels are elevated and also correlate well with the severity of the disease. Serum LDH and serum CPK levels are also higher indicating the underlying muscle injury seen in OP patients. They can be used for predicting intermediate syndrome and myopathy. Thus, biochemical parameters like serum amylase, serum LDH, serum CK can be used to assess severity of OP poisoning and for early identification of complications.

Future researches involving large cohorts and multiple centres need to be done in this area to understand the prognostic significance of serum Amylase and serum LDH in OP poisoning. Long term follows up studies using serial estimations can help in understanding the role of creatine kinase in predicting the onset of intermediate syndrome and delayed polyneuropathy

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