

A person wearing a full-body yellow protective suit, including a hood and gloves, stands in a field of tall grass. The person is facing away from the camera, looking towards a paved path in the background. The scene is outdoors with green foliage and a grey path.

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ARTICLE

**Lactate and creatine phosphokinase as potential independent predictors of organophosphorus poisoning severity in Zagazig University Hospital Patients, Egypt**

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Manar H. Arafa, Nashwa M. Shalaby and Hebatallah H. Atteia

*Full Length Research Paper*

# Lactate and creatine phosphokinase as potential independent predictors of organophosphorus poisoning severity in Zagazig University Hospital Patients, Egypt

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This study aimed to assess the correlation of serum lactate and creatine phosphokinase (CPK) levels, and their association with severity of organophosphorus poisoning in order to use one of them or both as tools in predicting prognosis. This study was conducted over one year and 68 organophosphate (OP)-poisoned patients were enrolled. Clinical severity of cases was categorized according to Peradeniya organophosphorus poisoning (POP) scale. Levels of serum acetyl choline esterase (AChE), serum CPK and serum lactate were measured on admission (0 h), 6 and 24 h post-ingestion. The results showed a high statistically significant difference between cases and control regarding AChE, CPK and lactate on admission. Also, there was high statistically significant difference regarding AChE, CPK and lactate among different categories of cases on admission, 6 and 24 h post admission. In addition, there was a statistically significant increase among different categories of POP scale regarding the quantity of atropine used in management of cases. Regarding oximes and stay in ICU, there was a statistically significant increase in severe poisoned patients when compared with moderate poisoned ones. A significant negative correlation was observed between AChE and severity of poisoning as well as significant positive correlation between CPK and lactate. It is concluded that serum CPK and serum lactate can be used as predictor of outcomes in OP poisoning and helps in determining cases that need follow up. Serum CPK and serum lactate can be used as predictors of outcomes in OP poisoning and helping in determining the cases that need follow up.

**Key words:** Organophosphorus poisoning, serum lactate, predicting prognosis, serum, admission.

## INTRODUCTION

The World Health Organization (WHO) estimates the incidence of pesticide poisoning to be three million cases per year, leading to more than 250,000 deaths annually (WHO, 2016). Organophosphate (OP) poisoning is

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considered to be a frequent reason for admission in hospitals and intensive care units (ICU) in developing countries (Senarathna et al., 2012).

Organophosphate (OP) insecticides are a group of insecticides acting on the enzyme, acetylcholinesterase (AChE). They irreversibly inactivate this enzyme which is essential for nerve function in insects, humans and many other animals. They also affect this enzyme in variable ways, contributing to their potential for poisoning (International Programme on Chemical Safety, 2016). Clinical features of OP are attributed to specific effects on muscarinic, nicotinic and central nervous system (CNS) receptors. This can result in diverse symptoms and signs (Peter and Cherian, 2000) depending on amount used and route of exposure (Eddleston et al., 2008). The common mode of presentation includes CNS symptoms which may include anxiety, confusion, seizures and coma. The muscarinic effects include diaphoresis, diarrhea, gastrointestinal cramps, urination, miosis, blurred vision, bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation and excessive salivation. Other muscarinic effects may include muscle fatigue, fasciculation, paralysis, respiratory muscle weakness, tachycardia and hypertension. Nicotinic features include fasciculation, paresis or paralysis (Sen et al., 2014). Cardiac arrhythmias, including heart block and QTc prolongation, are occasionally observed in OP agents poisoning (Wang et al., 1998). Late onset polyneuropathy can also occur following OP poisoning (Aygün et al., 2003; Genel et al., 2003).

The inhibition of AChE is the main mechanism of cholinergic crisis, leading to stimulation of both muscarinic and nicotinic receptors. Muscarinic effects include excessive salivation, lacrimation, urination, diarrhea, gastrointestinal cramps, vomiting, pupil constriction, blurred vision, bradycardia, as well as wheezes. Nicotinic manifestations include fasciculation and paralysis (Sen et al., 2014). Peradeniya organophosphorus poisoning (POP) is a simple scale used to assess the severity of poisoning based on the symptoms at presentation. Patients with a high score on the POP scale have a high rate of morbidity and mortality (Senanayake et al., 1993).

Elevation of lactate level is not clearly defined but most studies use range between 2.0 and 2.5 mmol/L (Kruse et al., 2011) whereas, "high" lactate has been defined to be more than 4 mmol/L in many studies (Howell et al., 2007; Cox et al., 2012; Shapiro et al., 2005; Callaway et al., 2009). On the other hand, the "normal value" may vary depending on the assay used. The terms lactate and lactic acid are often used mutually but lactate (the component measured in blood) is strictly a weak base while lactic acid is the corresponding acid. "Lactic acidosis" is oftentimes used clinically to describe the elevation of lactate level but should be reserved for cases where there is acidosis pH < 7.35 (Luft et al., 1983).

Creatine phosphokinase (CPK) is an enzyme present in

different tissues and cells. It catalyses the conversion of creatine and utilizes adenosine triphosphate (ATP) to create phosphocreatine (PCr) and adenosine diphosphate (ADP). It is checked in blood tests not only as a marker of damage of CK-riptide especially skeletal muscle, but also brain, photoreceptor cells of the retina, hair cells of the inner ear, spermatozoa and smooth muscle (Wallimann and Hemmer, 1994). Agarwal et al. (2007) reported elevated level of CPK in serum of poisoning patients and for this reason, it may be used as a biomarker of OP poisoning.

Lactate levels are often used as alternative indicator for severity of illness severity and to measure response to therapy. Many medications and toxins are associated with elevated lactate (Reade et al., 2012). Patients with elevated lactate levels may be at higher risk for significant morbidity and mortality, and need a systematic approach for both diagnosis and treatment (Andersen et al., 2013).

Although, till now, few researches have shown that serum cholinesterase (ChE) and CPK level estimations are useful in diagnosis of acute phase OP poisoning, they do not show any relation of these biomarkers to the severity of OP poisoning (Goswamy et al., 1994; Aygün, 2002). Therefore, this study aimed to assess the correlation between serum lactate and CPK levels and their association with the severity of OP poisoning, hoping to use these markers as predictors of OP severity, as AChE is a diagnostic tool but these are prognostic more than diagnostic; furthermore, their availability and cheapness is more than that of AChE in developing countries.

## MATERIALS AND METHODS

### Study population

This case control study was conducted on consecutive organophosphorus (OP) poisoned patients, admitted in Zagazig University Hospitals from December 2015 to November 2016. They were presented within 6 h of OP ingestion and were diagnosed with acute OP intoxication from history and clinical examination. The cases were suffering from nausea, vomiting, diarrhoea, salivation, urination, sweating, copious secretions, bradycardia, hypotension, miosis, wheezing, chest crepitation, weakness, fasciculation, cramps, paralysis, coma and respiratory failure. According to POP score (Senanayake et al., 1993), patients were classified into three categories based on clinical parameters: 0 to 3, mild poisoning; 4 to 7, moderate poisoning; 8 to 11, severe poisoning groups (Table 1).

### Exclusion and inclusion criteria

Patients who were presented later than 6 h of poisoning and those having diabetes mellitus, thyroid disease, chronic heart diseases and hepatic or renal failure, as well as patients subjected to cholinergic or sympatholytic drugs or any other medications for chronic disease were excluded. According to these exclusion criteria, only 68 OP-poisoned patients were enrolled in this study.

**Table 1.** The Peradeniya organophosphorus poisoning 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 to 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 commands	1
	No response to verbal commands	2
Seizures	Absent	0
	Present	1

They were (35) males and (33) females, with mean age of  $26.5 \pm 2.3$  years, presented within 6 h from the exposure to OP compound and had most of the previous clinical findings mentioned previously. All patients received airway control, decontamination, O<sub>2</sub> therapy and administration of antidotes; atropine and pralidoxime and other routine treatment. Seventy healthy individuals (age- and sex-matched) served as a control group. Informed consents from all patients and approval letter from the Ethical Committee for Research (Institutional Review Board 'IRB'), Faculty of Medicine, Zagazig University were obtained.

On admission to the emergency department (0<sup>th</sup> h) and at 6<sup>th</sup> and 24<sup>th</sup> h after admission, 5 ml of venous sample was collected from study participants. The blood samples were centrifuged at 3000 rpm for 10 min and serum was collected. Measurements of serum acetyl cholinesterase (AChE), CPK and lactate levels were performed and correlated with the severity of poisoning according to POP scale. The required treatments including atropine and oximes for management as well as duration of hospital stay were determined.

## Biochemical analysis

### Determination of serum acetyl cholinesterase

Serum acetylcholinesterase (AChE) activity was determined colorimetrically according to the method of Ellman et al. (1961). The reaction was done twice for each sample in the same time. Briefly, 4 ml solution containing 4 mM tris buffer (pH = 7.4), 40 mM MgCl<sub>2</sub>, 0.1 mM × 10<sup>-4</sup> M DTNB (colouring reagent), and 0.2 mM × 10<sup>-4</sup> M of S-butyrylthiocholine iodide (substrate) were pre-incubated at 37°C for 10 min with coupling. 20 µl of plasma samples was added into each tube of the aforementioned substrate solution. The mixture

was vortexed and absorbances of produced yellow colour were read spectrophotometrically at 1 min interval for 3 min at 412 nm. Blank was run parallel to each sample without addition of substrate. Activity was expressed as U/l.

### Determination of serum creatine phosphokinase (CPK)

Kinetic determination of CPK is based upon the fact that it catalyses the reversible transfer of a phosphate group from phosphocreatine to ADP. This reaction is coupled to those catalyzed by hexokinase (HK) and glucose-6-phosphate dehydrogenase (G6P-DH). The rate of NADPH formation can be measured photometrically, and proportional to the catalytic concentration of CK present in the sample (Gerhardt and Waldenström, 1979). The reaction was performed by addition of 40 µl serum to 1 ml of the working reagent by mixing and incubation for 2 min. Absorbances were read at 1 min intervals, thereafter for 3 min. The difference between absorbances and the average absorbance differences per min were calculated.

### Determination of serum lactate

Lactate is oxidized to pyruvate and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) by lactate oxidase (LOX). In the presence of peroxidase (POD), hydrogen peroxide reacts with 2,4,6-tribromo-3-hydroxybenzoic acid (THB) and 4-aminoantipyrine (4-AAP) to form a red quinoneimine dye. Serum L-lactate level can be measured colorimetrically where lactate is oxidized to lactate oxidase (LOX) to generate pyruvate and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) which then interacts with 2,4,6-tribromo-3-hydroxybenzoic acid (THB) and 4-aminoantipyrine (4-AAP) in the presence of peroxidase (POD) to

**Table 2.** Personal data among the control and OP cases groups.

Data	Group			
	Control group	Cases group	t	P-value (significance)
Age (years)	25.9 ± 3.5	26.5 ± 2.3	26.5	NS (> 0.05)
Sex (M/F)	37/33	35/35		

NS, Non-significant.

**Table 3.** Laboratory parameters of control and cases groups on admission.

Parameter	Group			
	Control (N =70)	Cases on admission (N=68)	t	P-value (significance)
Serum AChE (U/L)	9511.44 ±1533.21	2430.49 ±1137.9	30.58	HS (< 0.00001)***
Serum CPK (U/L)	92.4 ±18.15	345.4±128.6	16.05	HS (< 0.00001)***
Serum lactate (mmol/L)	0.586 ± 0.35	2.59± 0.7	21.08	HS (<0.00001)***

HS, Highly significant.

**Table 4.** Association between POP score and quantity of atropine required.

Atropine	Mild (n=22)	Moderate (N=16)	Severe (N=30)	F	P
Atropine (Number of ampoules)	2.6±1.3	19.4±4.4	45.54±7.5	401.29	< 0.0001***

\*Significant.

form a red quinoneimine dye. The color intensity of the former red dye is directly proportional to the lactate concentration and can be determined by measuring the increase in absorbance at 546 nm. The reaction was carried out by mixing 10 µl of serum with 1 ml of the working reagent. The mixture was then incubated for 5 min at 37°C (Field et al., 1996).

### Statistical analysis

The collected data were statistically analyzed using SPSS program version 15. Quantitative data were summarized as mean + standard deviation (X + SD). Qualitative data were summarized as percentage. Test of significance for qualitative data was  $\chi^2$  (chi-square) test. Test of significance for quantitative data was done using ANOVA and student t tests for comparison between groups' means. Pearson test was used to evaluate the correlation between two variables. Logistic regression analysis was performed to determine the independent predictors of variables. The significance level was considered at  $p$  value < 0.05.

## RESULTS

There was a non-significant difference between OP poisoned cases and controls regarding the personal data (Table 2). The results showed a high statistically significant difference between cases and control on admission regarding AChE, CPK and lactate levels (Table 3). Figure 1 shows that there was a high

statistically significant difference ( $p < 0.0001$ ) in AChE activity among different POP categories of severity: mild, moderate and severe cases on admission, 6 and 24 h post admission. As shown in Figure 2, a high statistically significant difference ( $p < 0.0001$ ) regarding CPK was observed among different POP categories of severity on admission, 6 and 24 h post admission. Figure 3 shows a high statistically significant difference ( $p < 0.0001$ ) regarding lactate among different POP categories of severity: mild, moderate and severe cases on admission 6 and 24 h post admission. There was a high statistically significant increase among different POP categories regarding the quantity of atropine used in management of cases (Table 4). Table 5 shows a highly significant increase in oximes used in treatment and duration needed for stay in ICU of severe cases when compared with moderate ones.

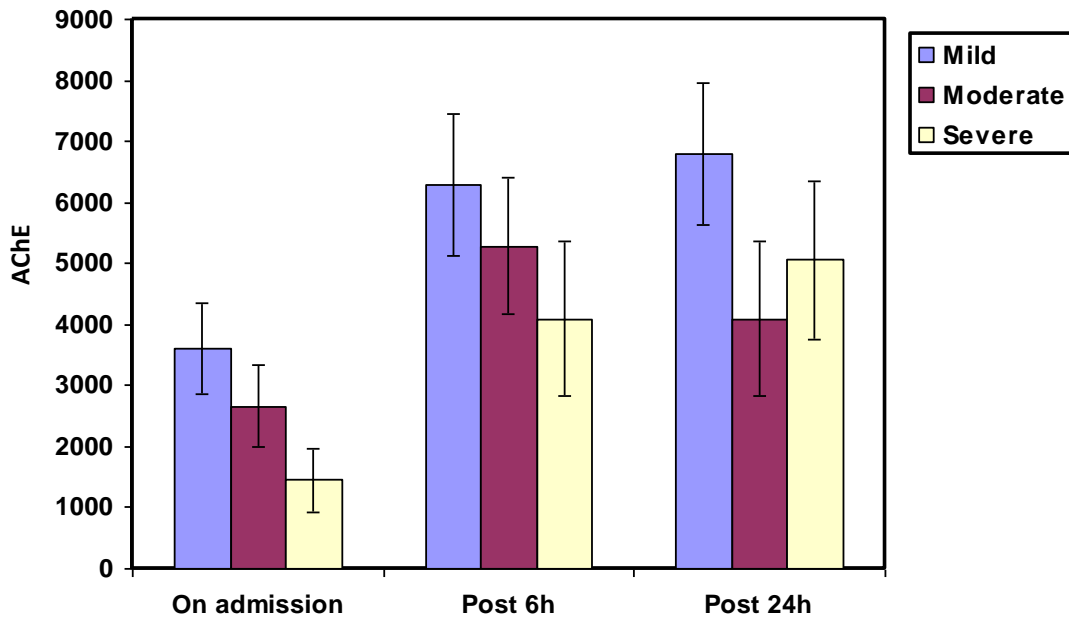
A negative correlation was observed between AChE and severity of poisoning while there was a positive correlation among CPK, lactate and severity of poisoning (Table 6 and Figures 4 to 6). When all significant variables (AChE, CPK and lactate) are introduced to multiple regression analysis (the model), the variables that remained significant (the strongest significant) in the model were lactate and CPK. Therefore, lactate and CPK seem to be significant determinant factors for prediction of OP poisoning (Table 7).



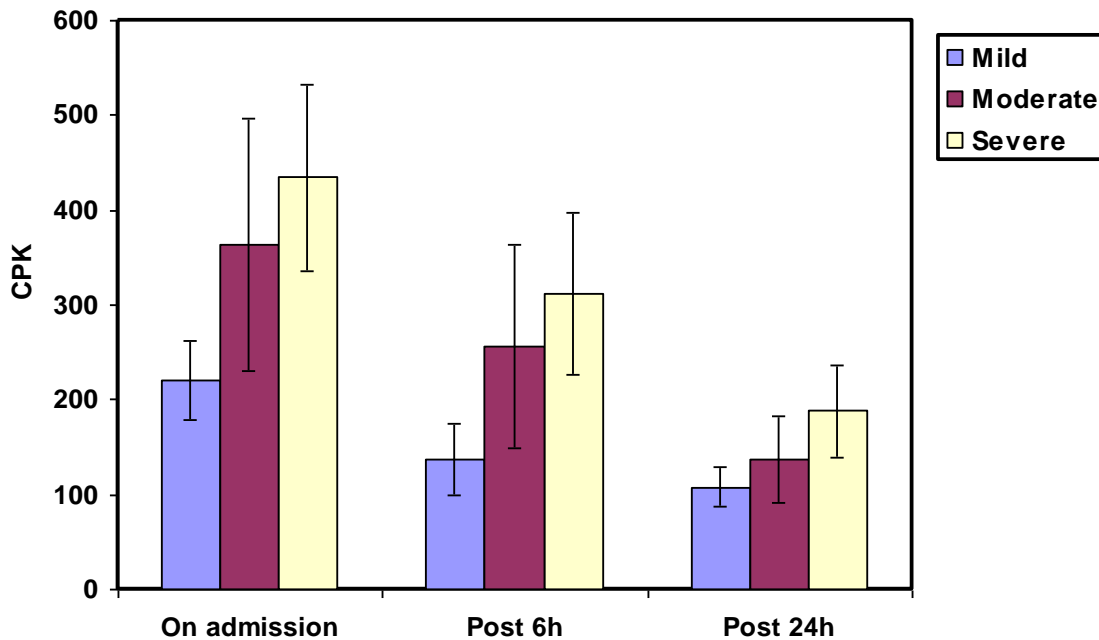
**Table 5.** Association between POP score and quantity of oximes required and duration of hospital stay.

Parameter	Moderate (N=6)	Severe (N=24)	t	P
Oximes	6.5 ± 1.4	17.5 ± 3.31	7.88	<0.0001***
Stay time in ICU	2.2 ± 0.68	7.1 ± 2.1	5.53	<0.0001***

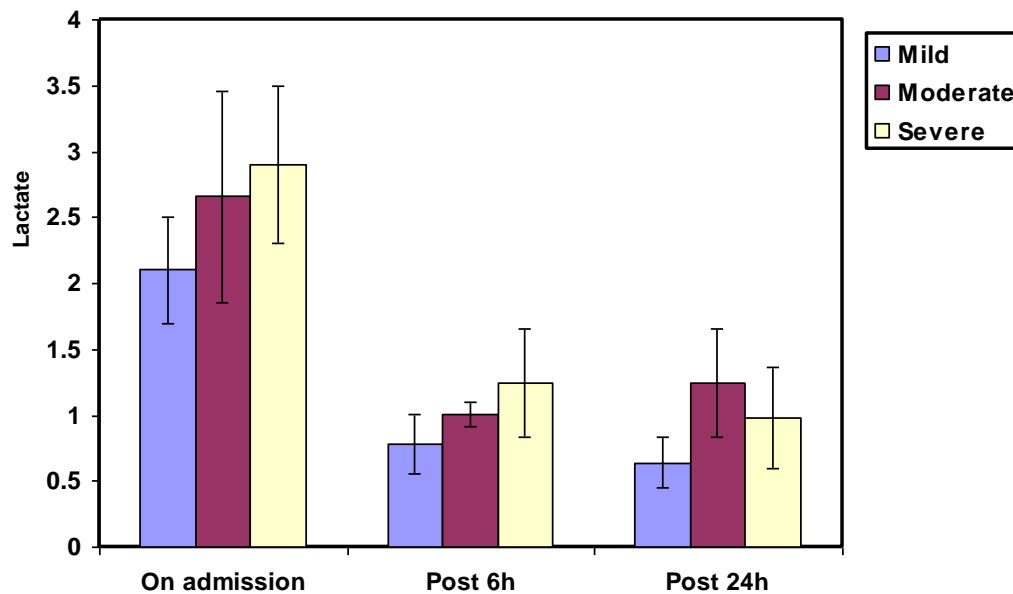
\*\*\*Significant.



**Figure 1.** AChE of the studied groups at 0, 6 and 24 h post admission.



**Figure 2.** CPK of the studied groups at 0, 6 and 24 h post admission.



**Figure 3.** Lactate levels of the studied groups at 0, 6 and 24 h post admission.

**Table 6.** Correlation between severity and other parameters.

Parameter	Severity	
	r	p
Cholinesterase	-0.35	<0.05*
CPK	0.69	<0.001**
Lactate	0.52	<0.001**

**Table 7.** Multiple regression analysis for factors predicting severity.

Parameter	$\beta \pm SE$	p
Lactate	0.0005 $\pm$ 0.00005	<0.001**
CPK	0.002 $\pm$ 0.0004	<0.001**

\*Significant.

## DISCUSSION

Organophosphate compounds are considered the most commonly used pesticides in agriculture field. Because it's wide usage and easy accessibility, poisoning with these pesticides has emerged as an important health hazard especially in developing countries (Han and Cui, 2010).

It has been shown by Senanayake et al. (1993) that the POP score can efficiently portend the severity, morbidity and mortality of OP poisoned cases. This scale uses elevated respiratory rate (>20/min) and the presence of cyanosis. This approach is likely to cause difficulties as severe OP poisoning may cause either central respiratory

depression with bradypnea, a reduced respiratory rate or tachypnea in the condition of bronchorrhea, bronchoconstriction or respiratory muscle weakness (Eddleston et al., 2006).

In this study, the results show a significant decrease in AChE activity with increasing degree of severity on admission, 6 and 24 h post admission as well as a negative correlation between AChE and severity of poisoning. In accordance with these results, Sen et al. (2014) concluded that serum AChE serves as a diagnostic parameter for OP poisoning and correlates with the severity but it cannot be used as a prognostic biomarker.

According to Bhattacharyya et al. (2011), CPK levels

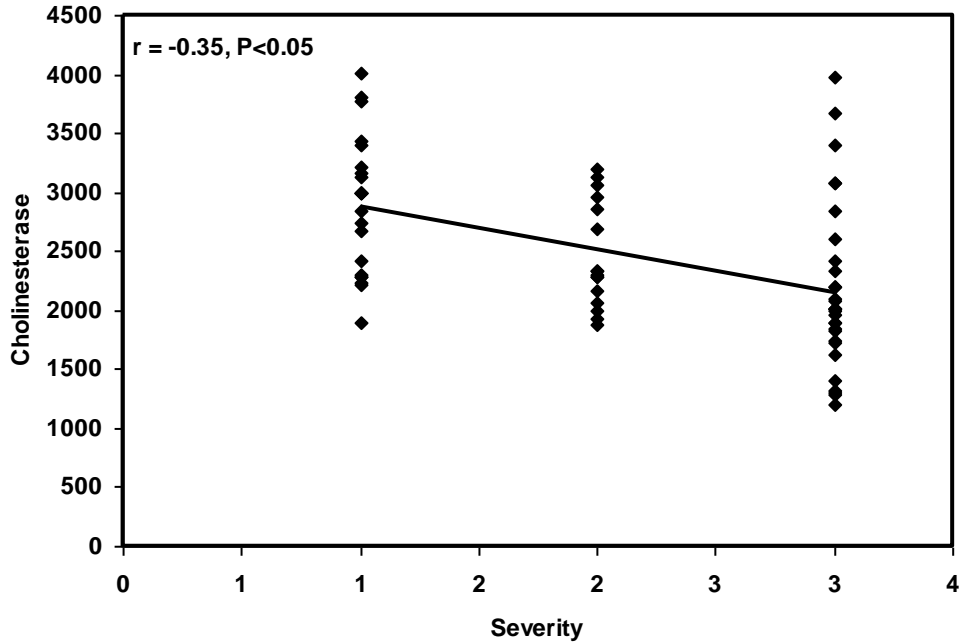


Figure 4. Correlation between AChE and severity in the study groups.

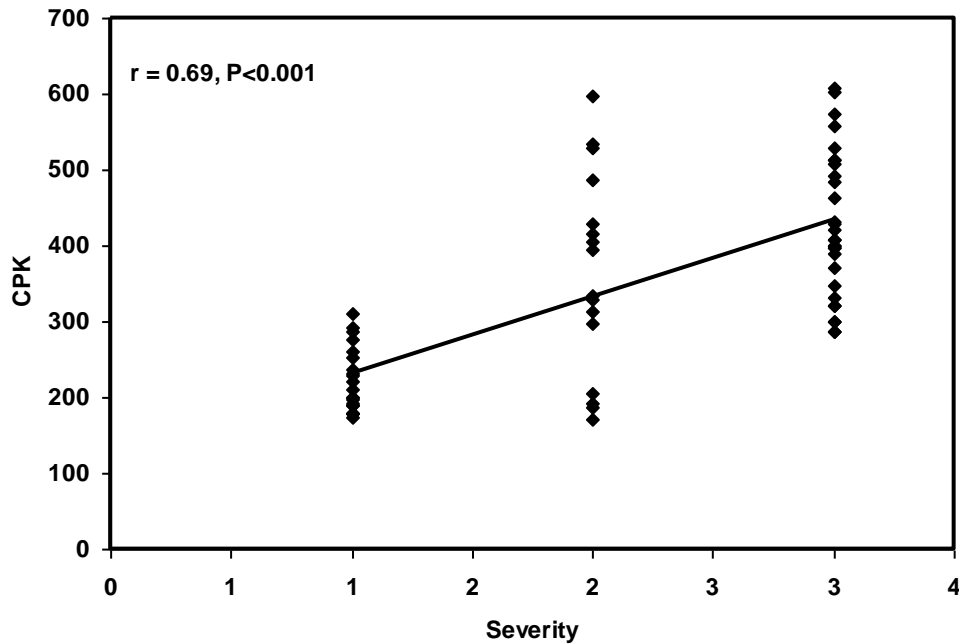
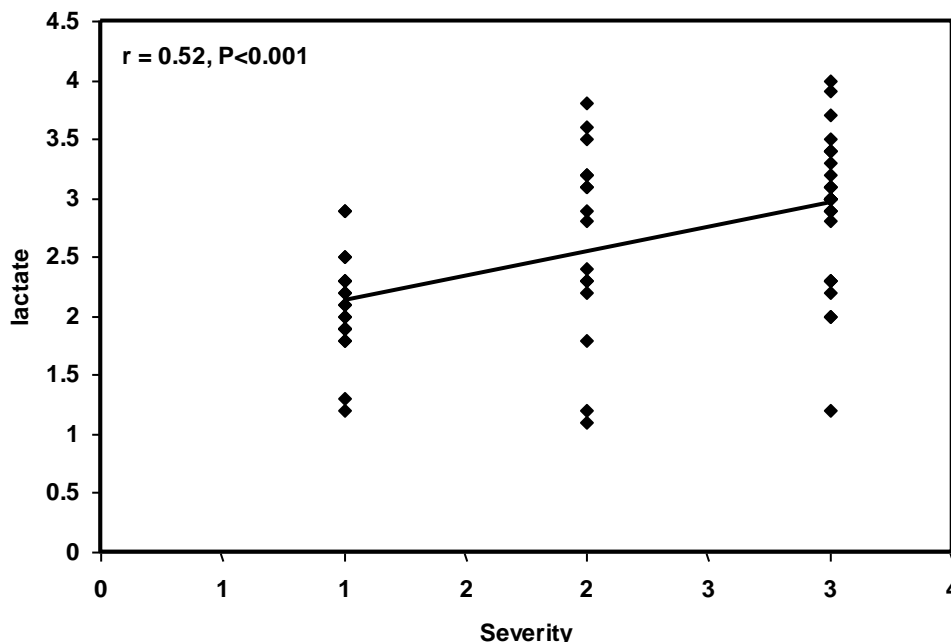


Figure 5. Correlation between CPK and severity in the study groups.

were correlated with the severity of the OP poisoning, as the severity increases, the CPK levels were increased and were found to be maximum in the severe form of OP poisoning. Sen et al. (2014) reported also that serum CPK shows a strong degree of positive correlation with the severity of poisoning and can be used as a predictor of outcome in OP poisoning. In line with this, serum CPK

results of this study showed that there were a statistically significant increase among different categories of severity (mild, moderate and severe) on admission, 6 and 24 h post admission as well as a strong positive correlation between CPK activity and the severity of poisoning.

Intermediate syndrome (IMS) is nominated because it occurs in the interval between the end of the acute



**Figure 6.** Correlation between lactate and severity in the study groups.

cholinergic crisis and OPIDN. Researchers have proven that IMS occurred between 48 and 96 h after acute poisoning and is recognized by weakness of proximal muscles of limb, neck flexors, respiratory muscles, and is attributed to necrosis of muscle fibers. Serum CPK rises in 6 h following muscle injury and continues to elevate for 5 to 6 days after injury. If there is outstanding injury to the muscle due to complications development, the CPK level continues to be elevated. Since half-life of CPK is about 1.5 days, it normalizes within 5 to 6 days of a single muscle insult (Sahjian and Frakes, 2007).

Cases with mild and moderate OP poisoning cases had elevated serum CPK level at least in one of the three serial measurements. This suggests that there is a direct relation between serum CPK levels and IMS. So, it is necessary for measuring CPK levels, especially after 48 h, in moderately to severely poisoned patients, so that IMS can be recognized earlier and patients can be referred to higher centers for immediate management of respiratory failure, reducing morbidity and mortality (Kumar et al., 2015). Bhattacharyya et al. (2011) showed that serum CPK level is elevated in severely poisoned patients even in the absence of IMS due to muscle fiber necrosis.

Generally, the mechanisms of hyperlactatemia including hypoperfusion lead to cellular hypoxia, increased activity of  $\text{Na}^+/\text{K}^+$ -ATPase in normoxia, increased pyruvate and lactate due to increased anaerobic glycolysis, decreased lactate clearance, muscle hyperactivity due to seizures, and impaired electron transfer and oxidative phosphorylation (Benaissa et al., 2003; Hulme and Sherwood, 2004; Jorens et al., 2004; Gunnerson, 2005).

Evaluation of the blood lactate level is generally used in diagnosis and management of the patients with signs and symptoms of sepsis or shock and is a sign of tissue hypoperfusion (Kompanje et al., 2007). The role of blood lactate level has been studied as a prognostic factor in drug and chemical poisoning too (Dell'Aglio et al., 2009; Seidowsky et al., 2009; Manini et al., 2010; Mégarbane et al., 2010; Inoue et al., 2008; Lee et al., 2012).

The current study detected a high statistically significant elevation in serum lactate levels with increased category of severity on admission, 6 and 24 h post admission as well as a strong positive correlation between lactate and severity of poisoning.

According to Lionte et al. (2016), lactate and Glasgow Coma Scale (GCS) can be used to predict morbidity and mortality after systemic poisons exposure. Tang et al. (2016) reported that 6-h post-admission high blood lactate levels, low blood pH, and low lactate clearance rates were independent prognostic factors identified for OP poisoning. This also keep up with Maignan et al. (2014), who stated that, some indicators such as toxicological history, GCS, QT interval, and serum lactate level, proved to be useful to distinguish between low and high acuity poisoned patients with deliberate drug poisoning, in order to avoid excessive morbidity after a retrospective analysis. In the same manner, Besli et al. (2010) identified a positive correlation between lactate and carboxyhemoglobin (COHb) levels and detected higher lactate levels in patients with neurological findings. Sokal and Kralkowska (1985) reported that lactate levels of patients with severe CO poisoning are significantly higher than mild poisoning. Inoue et al. (2008) reported also that initial lactate levels may be associated with

clinical course and outcome. So, they suggested that it can be used as a good marker for clinical course. Furthermore, Moon et al. (2011) suggested that the first lactate value is an independent factor for the change of mental status in CO poisoning and determining the need for intensive medical treatment, and it may be useful in predicting prognosis. In contrast to these results, Rishu et al. (2013) and Nichol et al. (2010) reported that blood lactate level has been reported to be a poor prognostic factor predicting death in hospital and ICU-admitted patients.

Regarding management of cases, doses of atropine used for patient's treatment here showed a high statistically significant increase among different categories of POP scale with increased degree of severity. Likewise, there was a highly significant increase in oximes doses used in treatment of severe cases when compared with moderate cases and also a significant increase in duration of stay in ICU between both categories. This coincides with the report of Rehiman et al. (2008) which showed that the total amount of atropine needed to treat patients and also mean duration of hospital stay increased with POP scale degree of severity.

## Conclusion

Serum CPK activity and lactate levels can be used as biomarkers in stratifying severity of acute OP poisoning, as they are cheap, easily available, especially in developing countries where EChE and BChE are not widely available in most of the laboratories. Also, serum cholinesterase levels have no prognostic value in acute organophosphate poisoning. Thus, a grading system to identify high-risk patients based on this measurement is most likely unreliable. The only disadvantage in using CPK activity and serum lactate level as predictors is that, the other causes of their elevation is strictly ruled out.

## Limitations

One of the limitations in the present study is that serial measurements were not done. To substantiate the findings, more multicentric studies with larger sample size has to be conducted.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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A person wearing a bright yellow full-body protective suit and black gloves is working outdoors. The person is bent over, possibly handling a sample or equipment. The background shows green foliage and a concrete path.

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