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Original Research Article

Evaluation of Serum Creatine Phosphokinase as a Marker of Severity in Organophosphorus Poisoning

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Abstract

Background & Objectives: Organophosphorus (OP) poisoning is an important global health problem. Estimation of erythrocyte cholinesterase (EChE) and butyrylcholinesterase (BChE) as an evidence of OP poisoning is costly and not regularly performed. There are emerging options for new cheaper biochemical markers in relation to OP poisoning like creatine phosphokinase (CPK). The objectives of this study were to measure serum CPK level and correlate it with severity of poisoning, to evaluate clinical and prognostic significance of CPK in OP poisoning, to assess if serum CPK level can be used as an alternative of BChE level to stratify OP poisoning severity.

Method: Total 100 patients of OP poisoning without any prior treatment, presenting within 12 hours, were selected and their clinical severity was categorized according to Peradeniya Organophosphorus Poisoning (POP) scale. Level of serum CPK, blood BChE and pH were measured and total dose of atropine required (mg) until final clinical outcome was calculated.

Results: Out of 100, 43% patients had mild, 36% moderate and 21% severe clinical picture. There was a significant positive correlation between serum CPK value and requirement of atropine dose in patient with severe POP scale category and negative correlation with pH and serum cholinesterase levels, indicating that more severe the poisoning more will be serum CPK and requirement of atropine doses while less will be pH and serum cholinesterase, ($p<0.0001$).

Conclusions: This study suggests role of serum creatine kinase as surrogate, relatively cheap and easily quantifiable markers of severe OPC exposure and their association.

Keywords: Atropine, Butyrylcholinesterase, Creatine phosphokinase, Erythrocyte cholinesterase, Organophosphorus, Peradeniya.

1. Introduction

Visual Organophosphorus (OP) toxicity is an important global health problem especially in many developing countries because of their widespread use and easy accessibility [1,2]. Major toxic mechanism of OP compounds are irreversible inhibitors of carboxylic ester hydrolases, including acetylcholinesterase (AChE), erythrocyte cholinesterase (EChE), plasma or butyrylcholinesterase (BChE) and other nonspecific proteases. The primary toxicity from these compounds is derived from excessive stimulation of muscarinic and nicotinic cholinergic receptors by the accumulated acetylcholine in the central and autonomic nervous systems as well as at skeletal neuromuscular junctions [3]. Furthermore, OP insecticides increase reactive oxygen species level which results in oxidative stress that contributes to cell membrane lipid peroxidation, DNA damage and cell death [4,5].

Laboratory evidence of OP poisoning is usually confirmed by measuring the decreases in the BChE and EChE activities. However, because of wide inter-individual variability, significant depression of the enzyme cholinesterase activity may occur but still fall within the "normal" range [6]. Also, estimation of either serum EChE or BChE levels is costly and not regularly performed in most laboratories [7].

There are emerging options for cheaper and/or easily quantifiable biochemical markers in relation to OP

poisoning like creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and serum immunoglobulins (IgG, IgA). But immunoglobulin assays, apart from being costly and difficult to perform in most laboratories, are often unreliable [8]. Several animal model studies proposed that serum level of CPK is often found to be elevated in OP poisoning, and it may be used as a biomarker [9].

Considering this background we planned a study to assess the correlation between serum CPK levels and the severity of acute OP poisoning. We tried to evaluate serum CPK level and correlate it with the severity of poisoning. Understand the clinical and prognostic significance of CPK in OP poisoning and to assess if serum CPK level can be used as an alternative of BChE level to stratify OP poisoning severity.

2. Materials and Methods

After obtaining Institutional Ethical Committee approval and written inform consent from patients, this prospective, observational study was conducted in 100 patients of either sex, having age >12 years, presented within 12 hour of ingestion or inhalation and were admitted in the Department of Medicine in Tertiary Care Hospital for a period of 2 year. The cases with indication of exposure to an entirely different poison other than OP poison, patients with OP poisoning and mixed with any other poison, chronic alcoholics patients, patients who had history of chronic liver disease, myopathy, history of malignancy, renal disease and history of intake of drugs like – statins, Fibrates, Dexamethasone, Aspirin, anticoagulants, frusemide were excluded from study.

Confirmation of OP poisoning was done by seeing the packet/container with clinical presentation. Clinical severity was categorized according to Peradeniya organophosphorus poisoning (POP) scale as shown in Table 1.

Table 1: Peradeniya organophosphorus poisoning (POP) Scale

POP Score	Severity	Number	Percentage (%)
0 – 3	Mild	43	43
4 – 7	Moderate	36	36
8 -11	Severe	21	21

After initial resuscitation and stabilization of patients, blood samples were collected aseptically by a single prick, from a peripheralvein without tying any tourniquet. The levels of serum CPK, serum cholinesterase and pH were measured following admission.CPK levels were estimated spectrophotometrically using the commercial kit of creatinkinase and by using UV kinetic optimized method. Serum cholinesterase (BChE) levels were estimated by using the reactivos GPL kit (Butyrylthiocholine Kinetic).

The blood pH was measured spectrophotometrically by EliTECH IRMA truPoint® blood gas analyzer (UK) Reference value (7.35 -7.45) at 37^0C [10].

After that patients were treated with 2–PAM (Pralidoxime) (adult dose 1 to 2gm Intravenously followed by 0.5gm/hour infusion.) and initial dose of atropine 2 mg followed by bolus every 5 to 10 min or as an infusion until the signs of "atropinization"- heart rate >80/min and dilatation of initially constricted pupil occurred. During treatment intramuscular injections were avoided. On the 3rd day and at the end of one completed week, the level of serum CPK was reevaluated and the response was tabulated. The total dose of atropine (mg) until the final clinical outcome (complete recovery or death) was calculated for each patient. Ventilatory support was given to the patients of apnea or obvious hypoventilation, persistent cyanosis or persistent tachypnoea (respiratory rate > 24/ min) along with deranged blood gases (PaO^2 < 60 mm, $PaCO^2$.>50 mm hg, ph< 7.2). The patients were followed up to death or discharge.

2.1 Statistical Analysis

The collected data were tabulated and analyzed using statistical software STATA version 13.1. Continuous variables were presented as Mean ±SD. Categorical variables were expressed in actual numbers and percentages. Continuous variables were compared between mortality and survival by performing independent t-test. Correlation of quantity consumed and time lag between mortality and survival by applying chi¯square test for linear trend. One way ANOVA was used to compare atropine total dose, pH, Serum cholinesterase and POP scale. Correlation coefficient (r) was used to assess the relationship between initial CPK level and POP scale, Serum cholinesterase, pH and Atropine dose. Correlation of ventilator support and outcome was assessed by performing chi¯square test. P-value of <0.05 was considered as statistical significance.

3. Observations and Results

Total 100 patients were enrolled in the study. Of them, 33 cases were in the 21 to 30 years age group, 28 cases were in 31-40 year age group, 7 cases were in above 60 age group and 5 cases below 20 years age group. The majority of cases (61) were between the age group 20 to 40 years. The incidence of organophosphorus poisoning was more in males (62) when compared to females (38). The main reason for majority of poison consumption was intentional 97% and only 3% had accidental exposure. According to POP scale 43% cases had mild poisoning and 36% cases had moderate while 21% patient were severely poisoned (Table 1). 19 out of 21 patients who were severely poisoned died (90.47%), while in moderate category 8 out of 36 patients died (22.22%). Table 2 shows the initial and final CPK levels according to the POP scores and the *P* value for each group.

Table 2: Comparison of Initial and Final CPK Level and POP Scale

POP Scale	Initial CPK Mean±SD	Final CPK Mean±SD	p-value
Mild	253.09±33.81	155.51±19.11	<0.0001, HS
Moderate	321.85±104.94	270.8±211.71	0.0200,S
Severe	568.77±162.34	576.66±249.48	0.8500,NS

HS: Highly significant, S: Significant, NS: Non-Significant

The reduction in CPK values with treatment in mild and moderate cases was significant, the changes in severe group was not statistically significant (p value 0.8500). The mean value of serum cholinesterase in mild, moderate and in sever group was 787.62, 703.77 and 549.42 respectively. On statistical comparison relation was found to be highly significant (p <0.0001) showing that low serum cholinesterase value was associated with higher mortality. Mean value of pH in mild, moderate and severe group was found to be 7.36, 7.31 and 7.09 while the mean value of atropine required was 352.55mg, 419.44mg and 464.76 mg respectively.

We found high degree of correlation between POP scale, arterial pH, total dose of atropine (mg) required, initial CPK level and serum cholinesterase level, (Table 3). Statistically the correlation was found to be highly significant (P < 0.0001) in each case. According to POP scale severity there was significant positive correlation between serum CPK value and requirement of atropine dose in "mg" in patient with severe POP scale category and negative correlation with pH and serum cholinesterase levels, indicating that more severe the poisoning more will be serum CPK, more will be requirement of atropine doses and less will be pH and serum cholinesterase.

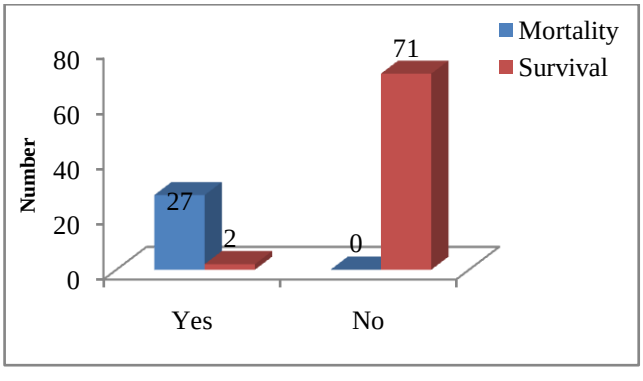
Table 3: Correlation of POP scale, arterial pH, atropine required, Initial CPK level and serum cholinesterase level

POP Scale	PH Mean±SD	Atropine Mean±SD	Initial CPK Level Mean±SD	Serum Cholinesterase Mean±SD
Mild	7.36±0.04	352.55±20.71	253.09±33.81	787.62±131.68
Moderate	7.31±0.13	419.44±93.19	332.91±122.89	703.77±123.50
Severe	7.09±0.15	464.76±129.36	632.33±125.54	549.42±72.60
F-value	44.79	14.66	112.84	28.42
p-value	<0.0001, HS	<0.0001, HS	<0.0001, HS	<0.0001, HS

HS: Highly significant, S: Significant, NS: Non-Significant

Out of 100 patients, 29 patients required ventilatory support out of which 27 died, 71 patients who did not required ventilator had no mortality. The P value was<0.0001 highly significant suggestive of patient requiring ventilatory support had higher mortality (Figure 1).

Figure 1: Correlation of ventilatory support and outcome



4. Discussion

The patients involved in the study had range between 11 to 70 years and 60% came from rural areas, whereas 40% were from urban areas. Low educational status, low socioeconomic status and poor living conditions in rural areas could be possible reason for poisoning.

The incidence of OP poisoning was higher in the age group 21 to 30 years followed by 31 to 40 years. Regarding occupation, 15% were students, 18% employee, 19% house wives, 30% labourer and 18% farmers. According to educational status 39 % patients were educated up to high school level and 27% were degree holders, 17% patients were illiterate and 17% were educated up to primary school. The most common route of exposure was oral route (98%) and only 2 % case was exposing to skin and inhalation. The main reason for majority of poison consumption was intentional 97% and only 3% had accidental exposure, these findings were similar to findings of previous studies[11-13]. The most common OP compound consumed was Monocrotophos 25% (25 cases) and followed by Chlorpyriphos (16%) and Dimethoate poisoning (15%). Selection of specific compound could be because of the wide variations in the cost and ease of local availability of compound according to crops grown in that area, or local industries producing such compound.

The accumulation of acetylcholine in nerve terminals, results in continued stimulation with subsequent paralysis of receptors. This is responsible for the clinical signs of OP compound poisoning. We observed muscarinic features where secretion in 53% patients, pin point pupils in 40% patients. The most commonly occurring nicotinic effect was muscular end plate block, resulting in muscle weakness (19%) and fasciculation (62%). The important CNS manifestation was depressed mental status seen in 27% of patients. Also, patients manifested with vomiting

(70%) and abdominal pain (39%), followed by seizers (7%), deranged sugar levels (16%) and diarrhea (27%). The metabolic acidosis was observed in varying degree in 44 patients (69.84%), respiratory paralysis in 10 patients (15.87%), coma in 7 patients (11.11%), inter mediate syndrome in 5 patients (7.94%), acute renal failure in 4 patients (6.35%) and arrhythmias in 2 patients (3.17%).

Out of 100 patients 27 patients expired. 43 patients were in the mild poisoning group none of them had died. Among the moderate poisoning group, out of 36 patients 8 patients expired, while in 21 severally poisoned patient 19 patients expired; so mortality increase as the POP scale severity increases. Eighteen patients land up in the intermediate syndrome out of 100 patients. 29 patients out of 100 required ventilator support out of which 27 expired. Two patients survived and discharged. Other complications like derangement of renal parameter occurred in 7 patients, 11 patients had complication of hypotension. Among those who died out of 27, 10 (37.03%) had aspiration pneumonitis, 9 (33.3 %) died due to cardiac arrest, 3(11.11%) patients having respiratory failure and 5 (18.5%) died due to ARDS. From the above findings we could see that respiratory failure was major cause of death occurring secondary to ARDS and aspiration.

The biochemical (Blood sugar, Serum creatinine and urea) results have not shown much variation from the normal levels, these findings were consistent with study conducted by Mahdi Balali-Mood *et al*[11].

The serum glucose changes in OP poisoning are usually clinically significant, as hyperglycemia has been reported in many studies in the literature. We too observed hyperglycemia in 20% (16 cases) of cases. The increase in serum glucose is believed to be due to the secondary release of catecholamines from the adrenal medulla. All these cases were not diabetic. Present study showed that there was a high degree of correlation between the initial serum CPK levels and the severity of acute OP poisoning. We found positive correlation of initial serum CPK level with POP scale and total dose of atropine in “mg”; whereas negative correlation of initial serum CPK with serum cholinesterase and pH. These correlations were found to be statistically highly significant, ($p<0.0001$). These results were in agreement with other studies [8,14].

Acidosis is a major predisposing factor that influences the severity of poisoning and outcome of patients [12]. Liu *et al*[15], detected that acid base interpretation was well correlated with the severity and mortality of acute OP poisoning. The mortality rate was lowest in the group of patients without acidosis and highest in the group with acidosis. We reported significant correlation between acidosis, CPK level and outcome. Presence of acidosis was associated with the raised serum CPK level and poor outcome as compared to those without acidosis and lower CPK level.

Acidosis itself can cause modest elevations in CPK levels in blood, which implies that CPK can be falsely high in case of acidosis [16]. However because acidosis is a relatively common complication in acute OP poisoning and can occur due to either hypoventilation or hypotension, CPK levels were also correlated with the degree of acidosis along with the severity of acute OP poisoning[17,18].

We also observed that serum CPK level was elevated in OP compound poisoning. Amount of rise depend upon the severity of poisoning. There was strong positive correlation between the clinical severity of poisoning and initial levels of serum CPK. There was significant correlation between day 3 CPK level and occurrence of intermediate syndrome. The present work highlighted the importance of serial measurements of serum CPK levels, as it might be helpful in predicting as well as assessing the prognosis of patients with acute OP poisoning. As follow up serum CPK levels measured in recovering patients without any complications during the therapy course showed a tendency to decrease. However who were severely poisoned and developed complications during the course of therapy, especially seizures and acidosis continued to remain elevated. This was in agreement with Sahjan and Frakes[19].

5. Conclusion

Organophosphorous poisoning was most prevalent in the age group of 21-30 years and incidence was more common in males. The elevated creatine kinase is commonly seen in OP compound poisoning and associated with high morbidity in terms of duration of hospital stay, respiratory depression, respiratory failure and higher mortality. We also concluded that higher the clinical grade of poisoning at initial presentation, more is the incidence of respiratory failure and need for mechanical ventilator support. High Serum levels of creatine kinase at admission indirectly indicate the severity of poisoning and poor prognosis. Early estimation of creatine kinase should be routinely considered as it is a good prognostic marker as well as marker in intermediate syndrome.

There is scope for large scale, multicentric studies to ascertain the role of serum creatinekinase as surrogate markers of severe OP compound exposure and their association.

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Reference

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