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Total serum creatine phosphokinase in assessing severity of OP compound poison

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Abstract
Background and Objectives: Poisoning has been found to be a major cause of death or morbidity in the developing world, the commonest being Organophosporus (OP) poisoning. Erythrocyte cholinesterase (EchE) and pseudocholinesterase (Butyryl cholinesterase – BchE) are markers used for assessing the severity in OP poisoning, but estimation of these are costly, has variable values for different individuals and are not available at all centers. This study was done to estimate levels of serum Creatine Phosphokinase (CPK) serially in acute OP poisoning patients and to correlate with Peradeniya Organophosphorus Poisoning (POP) score to predict the prognosis**.**
Methods: Patients with history of OP compound consumption who fulfil the inclusion and exclusion criteria, getting admitted at Shadan Intitute of Medical Sciences, during period of January 2014 to October 2016 is taken up for study.
Method of Collecting Data: One hundred cases of OP compound consumption meeting inclusion criteria will be undergoing detailed history, clinical examination and biochemical examination.
Information needed for this study collected through a proforma and pre-test proforma from each patient.
Results: In this study which included 200 patients of OP compound consumption, Bradycardia (33%) was the common clinical sign, followed by Hypertension (2%), Tachycardia (15%) and Hypotension (2%). The most common ECG finding seen was sinus bradycardia (31%) followed by sinus tachycardia (16%) and normal ECG (53%). Raised initial total serum creatine phosphokinase was 9%. Serial measurement of total serum creatine phosphokinase was done at day1, day3 and at discharge. All the 9 patients whose raised initial CPK level continued to be elevated at day 3 also. That means serial measurement of CPK level more important in assessing severity than the single value. It is well known that CPK level will raise at day3 if any ongoing intermediate syndrome due to rhabdomyolysis. Hence it is taken as confounding factor. But it is ruled out in this because all the 18 patients CPK level found to be high at day1. So CPK level will raise even in absence of intermediate syndrome.
The levels of CPK were elevated significantly in patients with respiratory failure. In this study 14 out of 16 patients with raised initial CPK level has respiratory failure and eventually death. Only one patient with mildly elevated CPK level has no respiratory failure. All patients who has initial raise of CPK level with only moderate decrement in plasma AchE is the valuable outcome in this study. Hence AchE cannot be a strong prognostic predicted as compared to total serum CPK level. The mean total serum CPK level of patients who went into respiratory failure and death was 1078 iu/l.
Conclusion: In this study only 8 out of 100 case shows raised total serum CPK level. 14 out of 16 positive case who developed respiratory failure and death. All 14 patients has marked raise in total serum CPK level. So the initial raise in total serum CPK level correlated well with severity of OP compound poison and prognosis, suggesting its use as a prognostic indicator of OP compound poison.

Keywords: Organophosphorus poisoning, total serum CPK level, plasma ache, tachycardia, bradycardia

Introduction
Poisoning has been known to be one of the leading causes of morbidity and mortality in the low and middle income countries of the world [1]. As it is cheap and widely available, organophosphorus (OP) compounds are most commonly used. 3 million deaths occur as a result of poisoning every year as stated by WHO [2]. They are used in agriculture to control pests, weeds, or plants diseases and also for suicidal purposes [3, 4]. These compounds act by inhibiting the enzyme acetylcholinesterase (AchE) which result in accumulation of acetylcholine at muscarinic and nicotinic receptors, producing an array of symptoms principal site being the peripheral nervous system [5].

After ingestion, symptoms usually appear within 30-90 minutes and a maximum of 24hrs in case of compounds which are highly lipophilic and which require metabolic bioactivation [6]. The acronym SLUDGE— salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis are often taught to associate OP poisoning. These symptoms do not usually prompt an emergency attendant to consider OP poisoning unless there is a definite history of OP exposure [7]. Deaths occur due to respiratory failure occurring in one of two distinct clinical syndromes: acute cholinergic respiratory failure or the intermediate syndrome. Delayed failure appears to be due to respiratory muscle weakness, but its pathophysiology is unclear [8]. Patients with acute OP poisoning are usually monitored by using serum AchE level which are expected to fall. It is not specific and does not correlate with the severity of poisoning and cannot be used as a prognostic indicator. There are emerging options for new cheaper and/or easily quantifiable biochemical markers in relation to OP poisoning like Creatine phosphokinase (CPK), lactate dehydrogenase (LDH), amylase and lipase [9]. Estimation of CPK is easy and levels are increased both in acute phase and in intermediate syndrome due to muscle fibre necrosis. It has been reported that high serum CPK levels reflect the magnitude of acute muscle necrosis and is the best and most sensitive indicator of muscle injury [10, 11].

Follow-up serum CPK level, measured in those individuals who were severely poisoned or those who developed complications, continued to remain elevated even after 1 week, whereas the values in recovering patients showed a tendency to decrease. The initial CPK level was also high in those who developed complications later on. So, serial measurement of serum CPK level might be helpful in predicting as well as assessing the prognosis of patients of OP poisoning.

Serum CPK level can be an efficient biomarker in case of acute OP poisoning not only due to its easy availability and low cost, but also because serial monitoring of its level during the entire course of therapy can predict the prognosis. However, the main disadvantage with this marker is its non-specificity. So, exclusion of other causes of raised CPK in a patient of acute OP poisoning is required.

Serum creatine phosphokinase can be a simple, cheap and widely available biomarker for acute OP poisoning. It can be of particular importance in developing countries, where other costly biomarkers are difficult to estimate.

Yves Vanneste and Dominique Lisson had shown that Rhabdomyonecrosis occurs after OP compound poisoning and was accompanied by a concurrent increase in serum CPK level and urinary creatine excretion rate.

In a study performed by John M, Oommer A, Zachariah A in CMC, Vellore, muscle injury was seen in all patient beginning at admission and peak over the first 5 days and then declining over next 5 days. Temporal profile of muscle isoenzymes of CPK showed significantly greater muscle injury in those patient with greater severity of poisoning at admission, those who developed Intermediate Syndrome and in patients with longer duration of Intermediate Syndrome.

Mechanism of raised total CPK level in op compound poison

The mechanism of AChE inhibitor-induced myopathy has been described as an agonist-induced myopathy with pre-junctional sarcoplasmic swelling and organelle damage, Z-band destruction and focal contractures. The CPK level will elevate even in the absence of IMS, provided the patient is severely poisoned, presumably due to muscle fibre necrosis

1. To study the changes in serum level of total creatine phosphokinase in assessing the severity of OP compound poison.
2. To study the prognostic significance of total serum creatine phosphokinase in patient with OP compound poison.

Methodology

Source of data

Patients with history of OP compound consumption getting admitted in SIMS, Hyderabad, during the period of January 2014 to October 2016 was taken up for study considering inclusion and exclusion criteria.

Methods of collection of data

1. Information will be collected through a proforma and pre-test proforma from each patient.
2. Qualifying patient will be undergoing detailed history, clinical examination and biochemical examination.

Type of study: Prospective observational study.

Sample size: 200

Inclusion criteria

Patient with definite history of OP compound poison and who actually produce the evidence of OP compound sample will be the study subjects.

Exclusion criteria

1. Patients with OP compound poison consumption along with any other poison like kerosene/alcohol.
2. Patient with indication of exposure to a entirely different poison other than OP compound.
3. Patient who are chronic alcoholics.
4. Patient with history suggestive of myopathy.
5. Patients with history of malignancy and autoimmune disease.
6. Patients with history of renal disease.
7. History of drug intake like steroids, statins, fibrates, etc.
8. Any trauma involving muscle.

Results

Table 1: Distribution of patients according to their age group (N = 50)

Age Group	Frequency	Percent
< 30	88	44.0%
≥ 40	44	22.0%
30 to 39	68	34.0%
Total	200	100.0%
Mean & SD		32.38 ± 11.25
Range		18-85

Table 2: Distribution of patients according to their sex

Sex	Frequency	Percent
Male	124	62.0%
Female	76	38.0%
Total	200	100.0%

This study conducted in K R Hospital between above mentioned period, showed incidence of OP compound poisoning common in males compared to females. Majority of patients were in the age group < 30 years with a mean of 32.38 ± 11.25.

Table 3: Distribution of patients according to the type of OP Compound consumed (N = 100)

Compound Consumed	Frequency	Percent
Chlorpyriphos	20	10.0%
Consumed	2	1.0%
Dimethoate	46	23.0%
Methyl parathion	24	12.0%
Phorate	60	30.0%
Quinolphos	48	24.0%
Total	**200**	**100.0%**

Most common compound consumed was Phorate (30%) followed by Quinolphos (24%).

Table 4: Distribution of patients according to their Peradeniya score (N = 100)

Peradeniya score group	Frequency	Percent
0 to 3	122	61.0%
4 to 7	60	30.0%
8 to 11	18	9.0%
Total	200	100.0%

Majority of the patients had a mild (61%) to moderate (30%) severity of organophosphorus poisoning at presentation, with 9% having severe poisoning.

Table 5: Distribution of patients according to the clinical features

Clinical Features	Frequency	Percentage
Hypertension	34	17.0
Hypotension	4	2.0
Tachycardia	30	15.0
Bradycardia	66	33.0

The most common clinical finding in patients was bradycardia (33%) followed by tachycardia (15%). Hypertension was seen in (17%) patients and hypotension (2%).

Table 6: Distribution of patients according to their ECG changes (N = 100)

ECG changes	Frequency	Percentage
Sinus Tachycardia	32	16.0
Sinus Bradycardia	62	31.0
ST elevation	0	0.0

Most common ECG finding was Sinus bradycardia (31%) followed by sinus tachycardia (16%) and normal is (53%). ST elevation is 0%.

Table 7: Distribution of patients according to their Total serum CPK changes (n=100)

CPK positivity (≥300U/L)	Frequency	Percentage
At Day 1	16	8
At Day 3	0	0
At Discharge	2	1

Table 8: Distribution of patients according to their acetyl cholinesterase levels

Acetyl cholinesterase level (IU/L)	Number	Percent
<2500	144	72%
>2500	56	28%

In this study 72% of patients with AChE level <2500 IU/L and 28% of patients with AChE level >2500 IU/L.

Table 9: Distribution of patients according to their duration of stay (N = 100)

Duration of stay in ICU in days	Number	Percent
<7	144	72%
>7	56	28%

Discussion

In this study 200 patients of organophosphorus poisoning who were brought to SIMS, Hyderabd with varying degree of severity were included and the total serum creatine phosphokinase in assessing severity of op compound poison is studied.

Age and Sex distribution

In this study patient in the age group ranging from 18 to 85 years were included with mean age of 32.38 ± 11.25. The highest number of patients were in the age group < 30 years (44%), followed by 30-39 years (34%), which is similar to that in other studies [60, 61].

The incidence of poisoning was more in males (62%) when compared to females (38%). This study correlated well with study done by Dash *et al*. study [12], which showed an incidence of 67% in males and 23% in females.

Organophosphorus compound

Phorate (30%) was the most common compound implicated in the poisoning. It was followed by quinolphos (24%) and dimethoate (23%). This was different from the study done by Karki P *et al*. [13] Who found the most common compound as Methyl parathion (23%) followed by Propoxur (5%), which can be explained by the difference in availability of compound in a particular geographic location. In 1 patients (1%) the compound was not brought and the patient was diagnosed and treated on the basis of clinical features.

Among the 8 patients who had were found to have raised initial total serum CPK level, Phorate was the compound in 3 patients, Methyl parathion in 2, Dimethoate in 2 and Quinolphos in 1 patient. Statistically significant relationship could not be established between the compound and raise in total serum CPK level.

Severity of poison

All the patients included in this study were classified according to the peradeniya organophosphorous scale (POP scale) into mild 0-3; moderate 4-7; and severe 8-11. Of the 100 patients who were studied 61% had mild, 30% had moderate and 9% had severe level of poisoning.

The mean age group in the mild (31.62±10.16 years) and moderate (33.15±10.7) were similar. However the mean age group in severe age group was 41.4±14 years. Suggesting that the older age group have a severe degree of poisoning. There was not much variation in the distribution of severity between males and females.

The severity correlated with reduction of plasma cholinesterase level, which showed a mean cholinesterase level of 2789.12 IU/L (±940.13) in mild, 2416.10IU/L (±1000.8) in moderate and 1150IU/L (±758) in severe. These values agree well with the study done by Kuntal Bhattacharya *et al*. [14] which showed a similar amount of AChE and increase in severity.

Clinical features and sign

Symptoms are classified into muscarinic and nicotinic receptors based on the receptors involved. Muscarinic features include excessive salivation, lacrimation, urination, diarrhoea, GIT cramps, emesis, blurred vision, miosis, bradycardia and wheezing. Nicotinic features include fasciculations, paresis or paralysis, hypertension and tachycardia. Central receptor features like confusion, seizures, anxiety, psychosis and ataxia. In our study Muscarinic features include bradycardia, hypotension and nicotinic features include hypertension and tachycardia are included because these signs can be well documented by our instruments, clinical examination and ECG.

Bradycardia (33%) was the common clinical sign seen in this study,which can be explained based on increased parasympathetic tone. Bradycardia was seen in 8 out 9 severe poison based on POP scale. Hence bradycardia can be considered as an indicator of severity of poisoning.

Blood pressure changes in the form of hypertension (SBP ≥140mmHg and/or DBP ≥90mmHg) and hypotension (SBP ≤90mmHg) were seen in 17% and 2% respectively. Two patients who developed hypotension did not recover and died after a prolonged ICU stay. This clinical feature were in agreement with the study done by Saadeh AM *et al*. [15]

ECG changes

The ECG reflects the widespread cardiac toxicity of OP compound. Ludromirsky *et al*. had described three phases of cardiotoxicity after OP poison. Phase 1-brief period of increased sympathetic tone, Phase 2-prolonged period of parasympathetic activity, Phase 3-QT prolongation followed by Torsades de pointes, VT and the VF. Both sympathetic and parasympathetic can cause cardiotoxicity. As we know that myocardial injury will raise CPKMB, part of total serum CPK. Thus ECG with ST elevation, ST depression, QT prolongation was put on exclusion criteria. In this study we used ECG only to document presence of sinus bradycardia, Sinus tachycardia and exclusion of ST elevation in the study.

In the current study abnormal ECG was noted in 47 cases. The most common finding in ECG is sinus bradycardia (31%) followed by sinus tachycardia (16%). The results was same with other studies. In the study done by Balouch *et al*. [66] and Sadeesh *et al*. [15] sinus bradycardia was the most common ECG finding when compared to sinus tachycardia.

Rise in initial total sreum cpk level

In this present study, raised total serum CPK level used as an indicator in assessing the severity of OP compound poison and its prognostic significance were positive (CPK ≥300 IU/L) in 8 out of 100 patients with mean value of 986.75 IU/L on day 1 of admission. This was similar to the study conducted by Kuntal Bhattacharya *et al*. 7 out of 8 patients who has significantly raised total serum CPK level died, it itself explain its prognostic significance and its role in assessing the severity of OP compound poison. Among the 8 patients who had found to have raised total serum CPK level, Phorate was the compound in 3 patients, Methyl parathion in 2 patient, Dimethoate in 2 patients and Quinolphos in 1 patient.

One patient with POP scale score 2 with raised initial total serum CPK (990IU/L) was expired due to respiratory failure. So CPK level has got more accuracy than any other clinical scale. Three patients with AChE 4300 IU/L with raised CPK level of 1009IU/L expired due to respiratory failure. So CPK level has got more prognostic significance than AChE. Raise in total CPK level with respiratory failure (mean CPK level 1080 [14]. IU/L with p-value 0.002). Raise in total serum CPK level with death (p-value <0.001). The presence of muscle fibre necrosis in OP compound poison has been already demonstrated in animal experimental studies by Calore *et al*. [14] A study conducted by Sharma *et al*. has shown that CPK was elevated in a fraction of their cases who had severe poisoning. It has been shown that there is rhabdomyolysis in intermediate syndrome and consequently raised CPK level.

But our study showed that serum CPK level is elevated even in absence of intermediate syndrome, provided the patient is severely poisoned, presumably due to muscle fibre necrosis. If there is ongoing injury to the muscle, the CPK level continues to be elevated. Since the half-life of CPK is about 1.5 days, it normalizes within 5-6 days of a single insult to the muscle.

It has been shown by Senanayeke *et al*. that the POP score can efficiently predict the severity, morbidity and mortality of OP poisoned patient. Also in our study, we found that sometimes POP score can be deceptive and even a patient with relatively low POP score can develop complications and/or death with raised total serum CPK level.

The quest for newer biomarkers in relation to OP poison started quite a long back time.OP labelled albumin in human plasma and blood have been suggested by some researches. Measurements of paraoxonase status, on the other hand, has been proposed as a reliable marker to assess susceptibility to OP poison [22-24]. Meconium and urine have also been studied for estimation of biomarkers in children susceptible to chronic OP exposure in utero [66]. These markers are costly and their estimation is difficult in developing countries.

Follow-up serum CPK level, measured in those individuals who were severely poisoned or those who developed complications, continued to be elevated even after 1 week, whereas the values in recovering patients shows tendency to decrease. The initial CPK level was high in those who developed complications later on. One patient in this study with mild elevation in CPK level (333IU/L) showed no complications later on due to poison and follow-up CPK at day 3 and at discharge shows the value tendency to decrease. So, serial measurement of serum CPK level might be helpful in predicting as well as assessing the severity of OP poisoning.

In our study, there was negative correlation (r=-0.227) between the severity of poisoning and serum AChE level and the correlation was statistically significant (p=0.001). This means that serum AChE can be a reliable marker for diagnosis. But compared value of survivors and non-survivors were not statistically significant. Suggesting it is not a reliable indicator for prognosis. So it can be used in diagnosing suspected OP compound poison at present without any prognostic significance. The comparative value

of serum CPK level between survivors and non-survivors showed statistically significant difference, suggesting it can be used as a prognostic indicator. To be more specific, if S. CPK persistently elevated above 900IU/L Throughout the course of disease, it is associated with higher rate of complication and mortality.

Conclusions

So, to conclude, serum CPK level can be a efficient biomarker in case of acute OP poisoning not only due to its easy availability and low cost, but also because serial monitoring of its level during the entire course of therapy can predict the prognosis. However, the main disadvantage with this marker is its non-specificity. So, exclusion of other causes of raised CPK in a patient of acute OP poisoning is required. Also, further studies with greater number of patients are required to support this study, since this study was conducted with a relatively small number of patients, and in one centre, which might prejudice any comment on its efficacy and reliability among other ethnic groups.

Key Messages: Total Serum CPK can be a simple, cheap and widely available biomarker for acute OP poisoning. It can be of particular importance in developing countries, where other costly biomarkers are difficult to estimate.

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