Clinical Profile of Acute Organophosphorous Poisoning with Special Reference to Serum Creatine Phosphokinase and Serum Lactate Dehydrogenase Levels as Prognostic Markers: A Tertiary Care Hospital Based Observational Study in North-East India

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ABSTRACT
Introduction: Organophosphorous compounds poisoning are a common cause of high morbidity and mortality in India owing to their low cost and easy availability. This study was undertaken to assess severity of organophosphorous compound poisoning clinically by using Peradeniya scoring & to assess correlation between serum Creatine Phosphokinase and Lactate Dehydrogenase levels with severity of acute OP poisoning.

Methods: We conducted a hospital based observational study comprising of 93 patients of Acute Organophosphorus Poisoning on basis of history of ingestion of organophosphorus compounds as said by the patient or attendant and with relevant clinical findings who had attended Medicine O.P.D/Casualty and was admitted in Gauhati Medical College and Hospital, Assam, India and fulfilled the inclusion and exclusion criteria. Statistical analysis was performed using GraphPad InStat version 3.00 for Windows 7, GraphPad Software, San Diego California USA.

Results: In our study, 51.61% were males and 48.39% were females. 35.48% was in second decade of life followed by third decade (30.12%). As assessed by POP Scale, 7.54% presented with most clinical severity (>8). 7.53% of total patients expired. 5.38% of expired patients had S.CPK level more than 1000U/L (p-value 0.0001). Of total patients expired, 6 (6.45%) patients had S.LDH levels less than 1000U/L and 1 (1.08%) patient had S.LDH level more than 1000U/L (p-value 0.259).

Conclusion: Early clinical assessment and grading according to Peradeniya Organophosphorous poisoning score correlated in predicting mortality. An association between Creatine Phosphokinase levels and higher rate of mortality was observed and this area needs to be particularly focussed.

Keywords: Organophosphorus Poisoning, Peradeniya Organophosphorus Poisoning (POP) Score, Creatine Phosphokinase, Lactate Dehydrogenase.

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INTRODUCTION
The World Health Organization (WHO) estimates that globally three million intentional or unintentional pesticide poisoning episodes occur annually and out of these a minimum of 300,000 die.¹ The incidence of Organophosphorous poisoning in India was around 1.26 lakhs during the period of 12 months in 2007, as reported by Ravi et al.² The most well-known compounds are malathion, parathion, fenthion, diazinon, dimethoate, chlorpyrifos, paraoxon and soman.³ They can be efficiently absorbed by inhalation, ingestion and skin penetration.⁴ They act by inhibiting the enzyme acetyl cholinesterase causing overstimulation of muscarinic and nicotinic receptors at the synapses in the central and peripheral nervous system, producing an array of symptoms like miosis, bradycardia, increased gastrointestinal motility, emesis, sweating, tachypnoea, salivation, lacrimation, altered sensorium, fasciculation, bronchospasm, blurred vision, urination and defeaecation. The complications include acidosis, respiratory paralysis, acute renal failure, seizures, arrhythmia, aspiration and death may be due to combination of one or above complications.⁵

Three types of neuromuscular paralysis are noticed. Type I is due to continued depolarization at neuromuscular junction, type II due to intermediate syndrome and type III due to delayed polyneuropathy. Central features include anxiety, confusion, seizures, psychosis and ataxia.⁶,⁷
Laboratory evidence of OP poisoning is usually confirmed by measuring the decreases in the butyrylcholinesterase (BChE) and erythrocyte cholinesterase (EChe) activities. Most studies have shown that though serum cholinesterase can be used as a diagnostic marker but its role is minimal as a prognostic marker. It has been seen that muscle fibre necrosis occurs with organophosphorous poisoning in both man and animals. Hence, parameters like serum creatine phosphokinase, serum lactate dehydrogenase, serum amylase, liver enzymes are considered as markers to see the correlation with severity and prognosis of organophosphorous poisoning. S. Agarwal et al. 2006, have reported that CK activity was significantly increased in poisoning cases (p≤0.01) and comparatively marked elevation was observed among the expired patients indicating cardiac functional impairment due to OP poisoning. S. Agarwal et al. 2006, observed that LDH activity was significantly elevated (p ≤ 0.01) in poisoning cases indicating muscular functional impairment due to organophosphorous toxicity. Clinical severity of poisoning can be categorized according to Peradeniya Organophosphorous Poisoning Scale as proposed by Senanayake et al. 1993.

**MATERIALS AND METHODS**

In this descriptive, observational study, conducted from 1st July 2015 to 30th December 2016, a total of 93 patients were included. These patients, all above the age of 13 years, had attended Medicine O.P.D./casualty and was admitted in the ward on basis of history of ingestion of organophosphorus compounds as said by the patient or attendant and with relevant clinical findings in Gauhati Medical College and Hospital, Assam, India. Patients with other co-existing illness (myopathy, chronic renal disease, epilepsy, myocardial infarction, myocarditis, autoimmune diseases or malignancy) or who had trauma or received intramuscular (I/M) injection and cardiopulmonary resuscitation recently or on prior medications like statins, fibrates, aspirin, anticoagulants, frusemide, and dexamethasone were excluded. Ethical clearance was obtained from the ethical committee of Gauhati Medical College & Hospital.

**Assessment**

Data was collected by interviewing the patient or attendants, thorough physical examination and relevant investigations. The diagnosis of acute organophosphorous poisoning was based on the following criteria: (1) history of ingestion of insecticide; (2) characteristic clinical signs and symptoms of OP poisoning; (3) improvement of signs and symptoms after treatment with atropine and oximes. Data was recorded in a preformed proforma. Informed consent was taken from eligible patients or legally authorized attendants (if the patient was unconscious). Medicolegal formalities were done. Clinical data mainly comprised of age, sex, time interval between ingestion of organophosphorus compound and presentation to the hospital, whether the act was suicidal/homicidal/accidental, cholinergic (muscarinic and nicotinic) manifestations. In clinical examination due importance was given to pulse, blood pressure, cyanosis, respiratory rate, heart rate, and neurological examination (special importance being given to eye examination). Data required were plotted in POP Scale for determination of severity.

For laboratory investigations, routine tests were done along with serum creatine phosphokinase and serum lactate dehydrogenase estimation by spectrophotometric analysis using Vitros350 and Vitros5600 Integrated system. The reference value for serum creatine phosphokinase was 55-170U/l and serum lactate dehydrogenase was 313-618U/l. For the purpose of study of mortality, serum creatine phosphokinase and serum lactate dehydrogenase values of 1000U/l were taken as the limit. Due to non-availability of equipments, estimation of cholinesterase levels could not be done. Apart from it chest X ray and ECG was done.

**Statistics**

All the statistical graphs were prepared using Microsoft Excel 2007 and Microsoft Word 2007. Statistical analysis was performed using GraphPad InStat version 3.00 for Windows 7, GraphPad Software, San Diego California USA. (www.graphpad.com).

**RESULTS**

Out of 93 cases, 48 (51.61%) were males and 45 (48.39%) were females. Male to Female ratio is 1.06:1. The age ranged from 13years to 70 years and mean age was 29.2±13.26 years. Majority (93.55%) of the cases were seen to consume organophosphorous compounds with an intention of suicidal attempt while only 6.45% of the total cases studied were found to be accidental.
Most of the cases (45.16%) of organophosphorus poisoning presented to the hospital within 2 to 4 hours of exposure to the poison while 40.86% of the cases presented after 4 hours of consumption of organophosphorus compound. Mean interval between consumption and admission to hospital was 3.8±1.35 hours. Of 93 cases, 63.44% presented with sinus tachycardia, 13.98% presented with sinus bradycardia, 11.83% with hypotension and 12.90% with hypertension. Most cases were found to be in confused state (35.48%) on CNS examination while 15.05% were unconscious, 2.15% with seizures and 3.23% with fasciculation. Tachypnea was found to be the most predominant respiratory feature (53.76%) in patients with OP poisoning, while 5.38% of the total cases presented with cyanosis. Also 9.67% of the total cases studied developed pulmonary oedema and 9.67% of the patients had respiratory muscle paralysis. Nausea and vomiting was the predominant symptom in majority of the cases (70.97%) followed by salivation (54.84%), while only 6.45% cases had diarrhoea. Majority (84.95%) of the patients had miosis at the time of presentation, 4.30% of the cases presented with diplopia and 18.28% of the patients had lacrimation.

According to Peradeniya criteria, 46.23% of total cases presented with mild severity, along with a similar percentage with moderate severity and 7.54% were presented with most clinical severity. Majority (5.38%) of the patients expired belonged to severe criteria marked by POP Scale. Only 2.15% patients of moderate severity had expired. No death had occurred in mild group. The statistical analysis test has calculated p value <0.0001 which is extremely significant.
Maximum number of patients (70.97%) had creatine phosphokinase levels between 171 to 1000 U/L. 17.2% of the cases had values less than 170U/L. While 11.83% of the cases had values more than 1000U/L. 86.02% of patients had S.CPK levels less than 1000U/L and 6 (6.45%) patients with S.CPK levels more than 1000 U/L have survived. While 2 (2.15%) patient with S.CPK level less than 1000 U/L and 5 (5.38%) patients with S.CPK level more than 1000U/L has succumbed to death.

Statistical Analysis Test has calculated p value of <0.0001 which is statistically significant 52.69% of the patients had serum lactate dehydrogenase levels below 618U/L. While 43.01% of the cases studied had serum lactate dehydrogenase levels between 619U/L and 1000U/L. Rest of the 4.3% had values more than 1000U/L. 89.24% patients of the total cases with S.LDH levels less than 1000U/L and 3 (3.23%) patients with S.LDH levels more than 1000U/L have survived. However, 6 (6.45%) of the patients with S.LDH levels less than 1000U/L and 1(1.08%) patient with S.LDH level more than 1000U/L had expired. Statistical analysis test shows p value to be 0.3500 which is insignificant.

**DISCUSSION**

**Gender Distribution**

In this study of 93 subjects, 48 patients (51.61%) were males and 45 patients (48.39%) were females with a male to female ratio of 1.06:1. Studies by S. Agarwal et al, 200610 and by Sahin COLAK et al, 2014 were also found male preponderance with 65.3% and 52.2% respectively.

**Age Distribution**

In this study, the youngest age was 13 years and the oldest age was 70 years with a mean age of 29.2±13.26 years. However, we had included only patients of 13 years and above in our study. Maximum number of cases were in the second decade of life (35.48%) followed by the third decade (30.12%) and fourth decade (17.2%). N. Saraf et al, 2014 found 46% of patients to be present in 3rd decade of life. Erkan Gonduz et al, 2013 observed a mean age of 27.29 ± 11.4 years in a study conducted in Turkey.

**Cause of Exposure**

Maximum number of patients 93.55% was exposed to organophosphorus compound with a suicidal attempt, the main route being ingestion as reported by their attendants. Of the total 93 patients, 6.45% were found to be accidentally exposed to organophosphorus compound as consequence of poor vision or improper placing of substances in kitchen. However, there was no history of suspicion of homicidal attempt nor any reported. In other studies also, poisoning with suicidal intent was found to be more common. This is in congruence with studies conducted by S. Agarwal et al 200610, I. Banerjee et al 200611, Sahin Colak et al 2014, Bhattachar et al 200520 with suicidal intent accounting for 80%, 82.2%, 67.2% and 87.2% respectively.

**Interval between Exposure and Admission to Hospital**

Majority of the cases studied 45.16% presented to the hospital within 2 to 4 hours of ingestion of the organophosphorus compounds with a mean interval of 3.8 ±1.35 hours. 40.86% of the cases came to the hospital after 4 hours of exposure. However, it is noteworthy to mention that cases presenting to hospital with history of consumption of organophosphorus compound within 6 hours were only included. The mean interval between poison consumption and admission to the hospital was 4.4 hours (Mean±S.D.: 4.4± 2.29) in a study by I. Banerjee et al.2006.15 In study conducted by P. Karri et al, 200417 maximum patients (90%) presented within 2 hours of consumption of organophosphorus compounds. Bhattachar et al, 200522 in a study conducted in Nepal reported time interval between ingestion and admission to hospital to be within 2 hours in 57.4% cases and between 2 to 4 hours in 29.8 % of the cases.

**Cardiovascular system Manifestations**

This study showed that 63.44% of the patients had Sinus Tachycardia while 13.98% had Sinus Bradycardia. 12.9% of the patients had hypertension while 11.83% presented with hypotension. N. Saraf et al, 2014 in a study conducted in Gulbarga had shown consistency with our findings; tachycardia (70%) being the most common manifestation. Cardiac manifestations observed in the study by S. Agarwal et al, 200610 include tachycardia in 24%, bradycardia in 6.6%, hypertension in 10.8% and hypotension in 2.4% owing to mechanisms of parasympathetic over activity and coronary spasm in addition to hypoxemia. Recent studies have shown tachycardia to be more frequent in acute OP poisoning, probably resulting from peganpilionic nicotinic receptor stimulation followed by release of adrenaline and nor-adrenaline from adrenal gland leading to pre-dominance of adrenergic activity of the heart.

**Central Nervous system Involvement**

Out of 93 cases, 33 (35.48%) of patients were found to be in confused state during the period of hospital stay while 14 (15.05%) of the cases were unconscious at presentation, 2.15% had seizures and 3.23% of the cases also developed fasciculation. G. Someswar et al, 2015 found disturbed consciousness in 72% of cases in a study conducted in Nandyal, thus showing consistency with our findings. However, they had shown 44% cases developing fasciculation. In contrast, S. Agarwal et al, 2006 found dizziness as the most common manifestation (95%) followed by confusion in 43%, coma in 1.6%,convulsions in 0.8%, fasciculations in 1.8%. N. Saraf et al, 2014 in a study in Gulbarga reported fasciculation in 56% of the cases.

**Respiratory system Involvement**

In this study, tachypnea was found to be the most predominant respiratory feature involving 53.76% patients with OP poisoning. Cyanosis was observed in 5.38% and bronchorrhea in 7.53% of the cases.

S. Agarwal et al, 200610 had shown Cyanosis in 2.4% and bronchorrhea in 21.6% of the cases in a study conducted in Ahmedabad. G. Someswar et al, 2015 have reported tachypnea as the major manifestation (86%) in patients in a study conducted by them. In a study by Makwava Prakash V et al, 2012 cyanosis was found in 14 % of the patients studied.

**Gastrointestinal Involvement**

Majority of the cases (70.97%) in our study presented with nausea and vomiting while 54.84% with salivation, and 6.45% cases had diarrhoea. S. Agarwal et al, 200610 reported vomiting as the dominant symptom in 97.4% of the cases while 78.4% had nausea, 62.5% had salivation and 35.6% had abdominal cramps. I. Banerjee et al, 2006 in his study had also shown consistency with our study as evident by majority (47.93%) of his cases had nausea and vomiting. Sahin Colak et al, 2014 in a study conducted in Turkey had also shown vomiting in 79% of cases, thus comprising majority.
Eye Involvement
In our study, 84.95% of the patients had miosis at the time of presentation. Out of 93 cases, 14 of the cases had pupil size more than or equal to 2mm, 46 i.e. majority of the cases had pupil size 1mm or less. Rest 33 of the patients had pupil size of less than 2mm but not pinpoint pupil. S. Agarwal et al, 2006\textsuperscript{16} in his study have reported pinpoint pupil in majority patients (66.1%). I. Banerjee et al, 2006\textsuperscript{18} has also shown predominance of miosis as the eye manifestation as it was evident in 91.94% of the total cases he had in his study. Makwava Prakash et al, 2012\textsuperscript{17} have however, shown pupil size of more than 2mm in 40 %cases, thus comprising majority of the cases and with 36% having pupil size less than 2mm in contrast to our study.

Clinical Severity and Prognosis on basis of grading of severity by POP SCALE
In the present study, 43 (46.23%) of total cases presented with mild severity, along with a similar percentage with moderate severity and 7 (7.54%) were presented with most clinical severity. The majority 5 (5.37%) of the patients expired belong to severe criteria marked by POP Scale. Two out of 93 patients (2.15%) of moderate severity expired. No death occurred in mild group. The statistical analysis test has calculated p value <0.0001 which is extremely significant. N. Saraf et al, 2014\textsuperscript{19} in their study had reported that 31 cases (96.9%) with mild grade poisoning (according to pop scale) survived. Only 1 patient (3.1%) in mild grade and (41.2%) in moderate grade had expired. There was only 1 case in severe grade which had also expired. This was statistically very highly significant (p < 0.001). This study hence, shows high compatibility with our study. Also in a study published in International Journal of Clinical Cases and Investigations had shown 50% of the cases studied in moderate severity, 5% in severe grade. 85% of the patients expired belonged to moderate and severe grade.\textsuperscript{19} Makwava Prakash et al, 2012 also had reported 75% of the cases of severe disease had expired.\textsuperscript{23}

Mortality
Out of 93 cases studied, 86 (92.47%) of the patients survived while 7 (7.53%) of the cases succumbed to death in our study. In a study by P. Karki et al, 2004\textsuperscript{17} and Makwava Prakash et al, 2012\textsuperscript{21}, mortality of the cases studied was reported to be 8.1% and 8% respectively which revealed similarity with our findings. In a study published in International Journal of Clinical Cases and Investigations, mortality was observed to be 18%.\textsuperscript{19}

Prognosis based on Serum Creatine Phosphokinase Levels
In the study conducted, majority 66 (70.97%) had creatine phosphokinase levels between 171 to 1000U/L while 11 (11.83%) of the cases had values more than 1000U/L. 80 (86.02%)patients with S.CPK levels less than 1000U/L and 6 (6.45%)patients with S.CPK levels more than 1000 U/L have survived. While 2 (2.15%) patients with S.CPK level less than 1000 U/L and 5 (5.38%) patients with S.CPK level more than 1000U/L have succumbed to death. Statistical Analysis Test has calculated p value of 0.0001 which is statistically significant. Almost similar incidence in a study done in Bhopal by R Sen et al, 2014\textsuperscript{24} also found that serum CPK in survivors was 698.58±486.48 U/L and non survivors was 1277.5±645.23U/L with p value of 0.002, which was statistically significant. S. Agarwal et al, 2006\textsuperscript{16} in a study done in Ahmedabad had also reported that Creatine Kinase activity was significantly increased in poisoning cases (p≤0.01) and comparatively marked elevation was observed among the expired patients indicating cardiac functional impairment due to OP poisoning. In his study, S.CPK levels were 104± 15.6 U/L in survived cases and 379± 53.7 U/L in expired cases. K. Bhattacharya et al, 2011\textsuperscript{11} in a study conducted in Kolkata had also commented the same.

Prognosis based on Serum LDH levels
In present series, 49 (52.69%) of the patients had serum lactate dehydrogenase levels below 618U/L. While 40 (43.01%) of the cases studied had serum lactate dehydrogenase levels between 619U/L and 1000U/L. Rest of the 4 (4.3%) had values more than 1000U/L. Of the total patients expired, 6 (6.45%) patients had S.LDH levels less than 1000U/L and 1 (1.06%) patient had S.LDH level more than 1000U/L. Statistical Analysis test showed p value to be 0.259 which was insignificant. Similar findings in a study by S.Agarwal et al, 2006\textsuperscript{10} was observed that LDH activity was significantly elevated (p ≤ 0.01) in poisoning cases indicating muscular functional impairment due to organophosphorus toxicity. S. LDH levels in patients who had survived were 217 U/L± 81.9, and those who had expired were 268 U/L±107.69.

CONCLUSION
This study focuses on the problem of Organophosphorous poisoning in our region. There is widespread abuse of these compounds probably because of their easy availability. Both muscarinic (bronchorrhea, bradycardia, hypotension, confusion) and nicotinic (tachycardia, hypertension, fasciculation, miosis, vomiting) manifestations were seen in the cases studied. Peradeniya Organophosphorus poisoning score of more than 8 correlated in predicting mortality. The Creatine Phosphokinase levels were significantly increased in poisoning cases and comparatively marked elevation was observed among the expired patients. Serum Lactate Dehydrogenase levels, however, did not correlate in predicting mortality in poisoning cases. Hence, estimation of Creatine Phosphokinase levels in suspected OP poisoning cases may serve as a corroborative prognostic marker. Also, appropriate medical management, an early recognition of its complication and increasing the awareness of organophosphorus compound toxicity would reduce the incidence of poisoning.

In our study, serum cholinesterase levels could not be estimated due to lack of equipment. Further, larger prospective studies with larger number of samples and with proven exposure to various organophosphorus compounds is necessary to arrive at a definitive conclusion.

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ANNEXURES

PERADENIYA ORGANOPHOSPHORUS (POP) SCALE

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Findings</th>
<th>Scale</th>
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<tr>
<td>Pupil size</td>
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</tr>
<tr>
<td>Respiratory rate</td>
<td>&lt;2mm</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate</td>
<td>≥20/minute</td>
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</tr>
<tr>
<td>Fasciculations</td>
<td>≥20/minute with cyanosis</td>
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</tr>
<tr>
<td>Consciousness</td>
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<td>Seizures</td>
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<td>Level</td>
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<tr>
<td>Present</td>
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<td></td>
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</table>

(0-3, Mild Poisoning; 4-7, Moderate Poisoning; 8-11, Severe Poisoning)

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