Lack of prognostic role for Glasgow coma scale, serum acetylcholinesterase and leukocyte levels in acute organophosphorus Toxicological ICU poisoned patients

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Abstract: Self-poisoning with organophosphorus (OPs) pesticide is a serious clinical problem across Asian countries. The aim of the present study was to assess the value of the Glasgow Coma Scale (GCS), serum acetylcholinesterase (SChE) and leukocyte on the length of stay and mortality due to OP poisoning as a prognostic value. We studied acutely OP-poisoned patients who had been admitted to the toxicological intensive care unit (TICU) of Loghman Hakim Hospital, from October 2010 to September 2011. Data including sex, age, cause of contact, ICU length of stay, muscarinic / nicotinic symptoms, initial Leukocyte, SChE and GCS levels were collected for under-study patients. Based on the patients' survival, they were divided into 2 groups, survivors and non-survivors (n=6). Thirty five eligible patients with a mean± SD age of 32.5±17 (range 2-72 years) were enrolled. Of these, 23(65.7%) were male. Suicide attempt was recorded in 31(88.6%) patients. Most of the patients had GCS above 10. The SChE ≥ 50% normal (≥1600 mU/ml) was reported in 45.7%. The mortality was 17.1% (n=6). The mean±SD and the median length of ICU stay in survivors were 7± 4 and 8. There was no statistically difference between the survivors and non-survivors according to the mean SChE, leukocyte and GCS. Only one dead patient had GCS lower than 10. (P>.05) Our results indicate that the GCS, SChE and leukocyte levels are not effective predictive factors for the outcome; however, they are useful in early diagnosis of OP poisoning.

Introduction: Self-poisoning with organophosphorus (OPs) pesticide is a serious clinical problem across Asian countries that have a great deal of agricultural activities(1-2). Low-cost and easy availability of OPs in developing countries such as India, Nicaragua and Iran make intentional and unintentional poisonings source (3). It is believed that between 750,000 and 3,000,000 OPs poisoning occur globally each year and estimated 200,000 die, annually, largely in the Asia-Pacific region(1, 4-5). They have also been used in terrorist or military attacks, as chemical warfare nerve agents (1). Nerve agent Tabun was used for the first time in 1984 by Iraqi army against Iran. From 1983 to 1988, Iraq used nerve agents such as Sarin and Tabun against Iranian combatants and the civilians (5).

OPs intoxication induces irreversible inhibition of acetylcholinesterase at the muscarinic and nicotinic synapses, due to inhibit the metabolism of acetylcholine (ACh). The accumulation of large amounts of ACh at the cholinergic synapses leads to acute cholinergic crisis, that it characterized by receptor overstimulation and a range of muscarinic, nicotinic, and central effects (6).

The severity of OP poisoning depends upon the toxicity potential of the agents, the kind of exposure and the time of treatment initiation (7). Immediate resuscitation, including circulatory support and mechanical ventilation is necessary in severely intoxicated patients (4).

This poisoning has high inpatient mortality and many patients have cardiorespiratory arrests after admission (8). Prognostic evaluation and estimation is very much critical and important for the outcome of treatment. There are limited studies in which the Glasgow Coma Scale (GCS), serum acetylcholinesterase and leukocyte have been mentioned as valuable prognostic factors (4, 7, 9-10).

The aim of the present study was to assess the value of the Glasgow Coma Scale (GCS), serum acetylcholinesterase and leukocyte on the length of
stay and mortality due to OP poisoning as prognostic and predictable outcome.

Materials and methods:
Acutely OP- poisoned patients who had been admitted within 24 hours after OP exposure to the toxicological intensive care unit (TICU) of Loghman Hakim Hospital Poison Center (LHHPC), from October 2010 to September 2011 were recruited in this cross-sectional study.

The hospital is a unique care teaching and referral poison treatment center in Tehran with nearly an annual average of 20000 hospital visits. Exclusion criteria were included: uncertain history of exposure, uncertain agent, transferring to other hospitals, carbamate poisoning and absence of initial SChE activity, WBC and GCS. Data retrospectively were collected from the patients' records by the study trained doctors, who filled the questionnaire including sex, age, time relapsed between exposure and admission to the hospital, cause of contact, muscarinic and nicotinic symptoms, Leukocyte levels (using the Sysmex KX-21 N Automated Hematology analyzer in Logman Hospital Laboratory), acetyl cholinesterase levels (spectrophotometric method using- Hitachi 911 autoanalyser in Logman Hospital Laboratory), GCS levels on admission and length of stay of these patients.

This study has ethics review committee approval from Shahid Beheshti University of Medical Sciences. The statistical analysis was performed with SPSS version 16 (SPSS Inc., Chicago, IL, USA). Data were analyzed through appropriate statistical tests, such as Chi-square test ($\chi^2$), and the Mann-Whitney U test. P-values equal to or less than 0.05 considered significant.

Results:
Based on the exclusion criteria, thirty five eligible patients from 100 admitted patients in Logman Hospital were enrolled in this study with a mean±SD age of 32.5±17 years (range 2-72 years). Of these, 23(65.7%) were male and 12 (34.3%) female. Mean estimated ingested dose was 100 ml (SD= 85).

Intentional poisoning for suicidal attempt recorded in 31(88.6%) patients and 4(11.4%) cases had accidental exposure. The median time relapsed between exposure and admission to the Hospital was 2 hours. (mean±SD = 6.5±16)

GCS of 31 patients were above 10 and 4 case had GCS between 3- 6. Seizure was recorded in 6 patients.

The SChE categorized in 3 groups which included: <20 % normal (≤640 mU/ml), between 20 to 50% (640 < & <1600 mU/ml) and > 50% normal (≥1600 mU/ml). (Table1)

Twenty three (65.7%) patients were intubated with or without mechanical ventilation during their ICU stay.

The most frequent muscarinic signs and symptoms were hyper salivation (42.9%) followed by miosis (40%) and vomiting (31.5%). (Table 1)
The mean dose of bolus atropine in patients' records was 8.0 ± 17.9 mg and the highest dose was 100 mg just in one case. Atropine was given during 5.3± 3.6 days (range 4 hours - 15 days) and the average infusion atropine dose was 132.9 ± 98.3 mg. A total of 26 (74.3%) patients received pralidoxime. The mean bolus pralidoxime dose was 1.4 ± 0.6 g. Pralidoxime was administered for 5.9 ± 5 days (range 2 hours-18 days) and the mean dose was 46.4± 31.6 g.

The mortality was 17.1% (n=6). Based on the patients' survival, they were divided in two groups, survivors (n=29) and non-survivors (n=6).

Comparison of complications between survivors and non-survivors showed 62.1% of survived patients had Intubation, while 83.3% of non-survived patients needed intubation during their ICU stay. Aspiration pneumonitis for the survived and non-survived patients was 34.5% and 33.3%, respectively. The mean±SD and median lengths of ICU stay of the survivors were 7± 4 days, and 8 days for non-survived patients.

The lowest level of cholinesterase was 180 IU/L and the highest leukocyte value was 18.9K/uL among the non-survivors group, whereas the mean acetyl cholinesterase level was 1576 IU/L and the mean leukocyte level 11.4 K/uL among the survivors. There were no statistically differences between the survivors and non-survivors according to the mean SChE and leukocyte levels (P>0.05).

There was no discernible significant difference in GCS between the survivors and non-survivor; only one patient had a GCS level of less than 10.

Discussion:
OPs poisoning is a major clinical entity and reason of considerable mortality and morbidity. Polyneuropathy as an important sequel is known in survivors. The range of mortality following organophosphate poisoning is estimated from 11 to 50% in literatures, while in our study mortality rate was 17.1% (9-12).

According to our previous study, low mortality rate in TICU might be due to high family and neighbors' attendance of the patient, as well as a shorter interval time between the exposures to toxin and admission to hospital. Mortality rate is not dose dependent but it depends on the toxicity potential(2).
In this study, the mean age of the cases was 32.5 years, which was lower than Basar Cander et al report (mean = 37.8)(7), but higher than Al B et al and his colleagues report (21 years)(13).

Acetylcholinesterase and butyrylcholinesterase enzymes were inhibited in the cholinergic synapse and plasma that leads to acetylcholine accumulation at the nerve synapses and neuromuscular junction. The over-stimulation of the acetylcholine receptors causes the clinical manifestations of Ops poisoning(4).

Relationships have been reported in different investigations between the severity of OPs poisoning and SChE. They reported that low SChE levels are correlated with a poor prognosis(14-17).

There are different methods and samples for measurement of cholinesterase. Some authors used separating red blood cell from plasma instead of whole blood (18-19). In the contrary, others reported that SChE is more preferable in the early detection of organophosphate toxicity than red cell cholinesterase (2, 20). Varies degrees of the SChE activity were detected in different individuals which are summarized in table 3. (7, 21-23)

Multi factors, such as hereditary deficiency of this enzyme, liver dysfunction, malnutrition, iron deficiency anemia, drugs like cocaine, morphine, codeine and succinylcholine decreased the importance of this enzyme as a biomarker in OPs poisoning.

In present study, we did not find any relationship between the acetylcholinesterase level at admission and prognosis prediction. Our results are in agreement with HW Yun et al statement in which was reported that a single measurement of SChE activity had no prognostic value (4). However, our findings are in contrary with the publication by Goswamy R et al(24).

Leukocytosis rates were reported between 30% and 76% for these patients in different studies (7, 25-26). Although, non-survivors patients in our study had a higher leukocyte level but there was no statistically significant differences between leukocyte levels and patients' outcome. Likewise, Cander B et al have found an increase in leukocyte levels of died patients, but without any statistically significant correlation with the prognosis (7).

Jennett and Teasdale described GCS as a scoring system for the evaluation of the patients' neurological condition, particularly in head trauma. Also in 1978, it was considered as effective parameter for definition of prognosis in nontrauma patient. Also low GCS value is considered as the result of central nervous system hypoperfusion in OP poisoning (7).

In the present study, most of the patients had GCS above 10 and no statistically differences were found between the GCS and patients' outcomes. Davies et al reported that intensive monitoring and treatment were necessary in the cases with a GCS value under 13 but 50% dead patients had mild symptoms on admission. Therefore, they suggested that monitoring and treatment must be performed immediately in asymptomatic OP poisoned patients (27).

Cander B et al found only a statistical correlation between GCS values and mortality (7).

In our study, the average infusion atropine dose was 132.9 ± 98.3 mg (during 5.3± 3.6 days), which was lower than Chaudhary SC et al report (509.17 ± 48.9 mg) (28). On the contrary, in the Sungur M and Güven M study, atropine was administered during 3.4 ± 2.1 days and the average total atropine dose was 79.1 ± 62.9 mg. (29).

In the present study, the mean bolus and infusion paralidoxime dose was 1.4 ± 0.6 g and 46.4± 31.6 g, respectively, while in the Eddleston M et al cohort study, the patients received pralidoxime chloride as a 1-g bolus followed by further 1-g bolus doses every 6h for 1–3 days (30).

**Conclusion:**

Our results indicate that the GCS, SChE and leukocyte levels are not effective in predicting the outcome but they are useful in early diagnosis of OP poisoning.

| Table 1: OP poisoned patients' serum cholinesterase activities (SChE) in admission time |
|---------------------------------|---------------------------------|-----------------------|
| Patient                         | SChE ≤20% Normal (≤640 mU/ml) | Between 20 to50 % Normal (640< & <1600 mU/ml) | ≥50 % Normal (≥1600 mU/ml) | Total |
| Number (%)                      | 12(34.3)                       | 7(20)                 | 16(45.7)                  | 35(100) |
Table 2: Muscarinic/nicotinic signs and symptoms of the patients

<table>
<thead>
<tr>
<th>Muscarinic signs and Symptom</th>
<th>Patient Number (%)</th>
<th>Nicotinic signs and Symptom</th>
<th>Patient Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper salivation</td>
<td>15(42.9)</td>
<td>Fasciculation</td>
<td>2(5.8)</td>
</tr>
<tr>
<td>Tearing</td>
<td>9(25.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miosis</td>
<td>14(40)</td>
<td>Muscle Weakness</td>
<td>6(17.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11(31.4)</td>
<td>Paralysis</td>
<td>1(2.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5(14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>7(20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brady cardia</td>
<td>6(17.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rales or wheeze</td>
<td>2(5.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Serum cholinesterase activities (SChE) in different study

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of the patients</th>
<th>Mean SChE± SD* (U/L)**</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cander B et al.,</td>
<td>25</td>
<td>Survived patients(n=22)3841 Death patients (n=3) 1768</td>
<td>7</td>
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<tr>
<td>Shadnia S et al.,</td>
<td>42</td>
<td>3900±330</td>
<td>22</td>
</tr>
<tr>
<td>Kavalci C et al.,</td>
<td>13</td>
<td>2945.1±2648.9</td>
<td>23</td>
</tr>
<tr>
<td>Brahni N et al.,</td>
<td>42</td>
<td>1260±2204</td>
<td>24</td>
</tr>
<tr>
<td>Nouira S et al.,</td>
<td>30</td>
<td>Low severity (n=18) 448 ± 409 High severity(n=12) 611 ± 575</td>
<td>25</td>
</tr>
</tbody>
</table>

*=Standard deviation, **= Unit/ Liter.

References
13. Al B, Güllü MN, Küçükköner M, Aldemir M, Güloğlu C. Demographic features of patients resorted to the dicle university medicine faculty