Original Article

Correlation of Clinical Score and Serum Acetylcholinesterase Level as a Predictor of Outcome among Patients with Acute Organophosphate Poisoning Admitted in Emergency Ward of a Tertiary Hospital

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Abstract

Background: Monitoring a patient's serum acetylcholinesterase (AChE) status after clinical score of organophosphate poisoning enables the verification of exposure to anticholinesterase agents.

Methods: A cross-sectional study was conducted among the patients fulfilling the inclusion criteria and was categorized according to POP (Peradeniya Organophosphorus Poisoning) score. The study was conducted at a tertiary hospital for one year in the period of Jan 2016 to Dec 2016. POP score was applied and serum acetylcholinesterase level was determined in the lab. Spearman's rho coefficient method was applied for correlation.

Results: Seventy four patients survived in emergency ward who presented within (4.1 ± 2.9; 95% confidence interval [CI], 3.43- 4.80; *P*= 0.021) hours of ingestion of OP compounds, POP score 3 (Q1, Q3, 2, 4), serum AChE 2221 (Q1, Q3, 768.5, 4703.5) IU/L with 9 (Q1,Q3, 8.75, 34.75) mg of atropine used, 94% received PAM for 5 (Q1, Q3, 3, 7) days of hospital stay.

Four patients died within (7.5 ± 5.4; 95% CI, -1.16- 16.16; *P*= 0.021) hours of presentation, POP score of 4 (Q1, Q3, 4, 7.75), serum AChE 588 (Q1, Q3, 173, 1912) IU/L, atropine used 170 (Q1, Q3, 152.5, 297) mg, 5.1% received PAM for 3.5 (Q1, Q3, 1, 11.25) days of hospital stay.

Spearman's rho coefficient showed well correlation between POP score and serum AChE level (coefficient -0.356; *P*= 0.001), POP score for the need of atropine (coefficient= 0.536; P= 0.001).

Serum AChE also correlated with the length of hospital stay (coefficient= 0.414; P= 0.001) compared to POP score (coefficient= 0.420; P= 0.001).

Conclusions: The higher degree of POP score correlated to higher degree of serum acetylcholinesterase derangement, need for atropine, PAM and length of hospital stay. Thus, it enhances in the prediction of outcome among patients with acute organophosphate poisoning at index visit.

Keywords: Acute organophosphate poisoning, peradeniya organophosphorus poisoning score, serum acetylcholinesterase level

Introduction

Organophosphorus (OP) insecticide self-poisoning is a major global public health problem[1] recognized to be confined to the developing countries in the Asian region with more than 300,000 deaths each year around the world[2].

OP compounds are important insecticides used in agriculture and are possibly the most common causes of deliberate self-harm among adolescents and young adults in developing nations.[3-8]

The total number of death from OP compound was reported from 16.7% to 50% among hospitalized patients. The decline in the proportion survival rate was reported to be 67% during the first three days in intensive care[9,10] which demonstrates its seriousness as a global health problem.

POP (Peradeniya Organophosphorus Poisoning) score was developed in Department of

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Medicine, Faculty of Medicine, University of Peradeniya, Sri Lanka in 1993 with the aim to assess the severity of OP intoxication. POP scale includes five common parameters of OP poison (respiratory rate, pulse rate, pupil size, level of consciousness, seizure activity and fasciculation). Presence of each parameter scored from zero to two at initial presentation. The severity is graded as mild (score 0- 3), moderate (score 4- 7) and severe (score 8- 11). The POP score is a well validated scale which correlates with death, the need for ventilatory support and the dose of atropine required.[11]

Various studies have demonstrated the utility of POP score to predict morbidity and mortality.[12-15] POP score can, thus, be useful especially in settings with relative resource constraints.

Acetylcholinesterase (AChE) enzymes are inhibited by OP compounds resulting in overstimulation of muscarinic and nicotinic receptors.[16] The cholinergic syndrome appears when approximately 50% of serum AChE is inhibited and death is believed to occur when serum AChE appeared to be inhibited to more than 90% from its normal.[17] Inhibition of AChE is regarded as the primary toxic mechanism of OP poisoning.[18] A study from Nepal showed that serum AChE is useful to predict severity of poisoning, atropine use and length of hospital stay (LOS).[12] OP compound poisoning is a common problem in our emergency with diverse set of presentations.

With a lesser than regular availability of AChE and preexisting laboratories issues in a resource constrained setting at primary hospital care, it poses a continual challenge to doctors working in those setup hospitals to decide the need of atropine as well as supportive treatment and counseling about the prognosis. Hence, serum AChE and POP score correlation was a useful tool in deciding the severity and prompt management of acute OP poisoning cases.

We designed a study to compare and correlate the POP score with serum AChE levels in acute OP poisoning. The secondary objectives were to describe the outcome and the requirement of atropine and pralidoxime.

Methods

Study type

A cross-sectional observational study was conducted from Jan. 2016 to Dec. 2016 in patients presenting in emergency ward of a tertiary hospital with history of acute organophosphate poisoning.

Setting

The study was carried out in emergency ward of a tertiary hospital in eastern Nepal. It is 800-bedded tertiary hospital with 85 beds in emergency ward, with specified areas i.e. area A with 4 beds, area B with 4 beds, area C1 and C2 with 50 beds, area D with 5 beds and area E with 22 beds respectively and average rate of approximately 100 patients per day. Emergency ward care is provided 24 hours a day, serving more than 40,000 patients a year.

Participants

All the patients presenting with OP poisoning were eligible for the enrollment in the study. An informed consent with voluntary participation was collected from all the patients participating in the study. Due to legal obligation, consent was taken also from legal guardian in case of unstable patients or those who couldn't communicate due to severity of poisoning. The enrollment criteria were a definitive history of OP poison plus its characteristic clinical manifestation or other evidence of poison intake like poison container. The typical characteristic features of OP poisoning also included:

diarrhea, urination, miosis, bronchospasm, emesis, lacrimation, and salivation[5] and was not exclusive to only POP score parameters i.e. pupil size, respiratory rate, heart rate, fasciculation, level of consciousness and seizures. Those typical characteristics were also considered helpful as study enrollment criteria.

The POP score was calculated immediately after arrival during the period of resuscitation and initial physician evaluation. A score of less than 3 was considered as mild poisoning, 4 to 7 moderate and 8 to 11 severe poisoning (Additional file 1). Once the characteristic features of OP poisoning were identified, serum AChE was sent immediately, along with other blood studies. The normal range of serum acetylcholinesterase was 3167 to 6333 IU/ L as per our laboratory criteria for both the genders. Those patients with incomplete data, inability to verify the type of poison and mixed poisoning were excluded from the study.

The calculated sample size was 92 considering the Pearson correlation coefficient value of 0.669 [12] at 95% confidence interval (CI) and 80% power which was rounded off to 100 to allow for non-response rate. The formula used was $N = [(Z\alpha+Z\beta)/C]\ 2 + 3$, where standard normal deviate for $\alpha = Z\alpha = 1.960$ and the standard normal deviate for $\beta = Z\beta = 0.842$. $C = 0.5 * \ln [(1+ r)/(1- r)] = 0.297$.

Blood collection procedure

After obtaining an informed consent, about 2 ml of venous blood was collected in plain glass tube under aseptic precautions. Blood was then allowed to clot, serum separated by centrifugation and used for estimation of plasma cholinesterase.

Outcomes

The primary outcome measure was the level of serum AChE and POP score. The secondary outcome measures were mortality and other patient outcomes, such as: survivors after poisoning, time of presentation, length of hospital stay and the use of atropine and pralidoxime.

Statistical analysis

The completed proforma forms were analyzed as per the study objectives (Additional file 2).

The data obtained were entered in a microsoft excel spreadsheet and analyzed. Statistical Package for the Social Sciences (SPSS) version 11.5 was used to carry out the descriptive and inferential statistics.

All the values are expressed as percentage, mean, SD, median interquartile range (IQR). Independent Sample t Test or 1-way analysis of variance was used to determine mean differences between two survivor and non-survivor groups. The χ^2 test was applied to compare differences in the results of quantitative variables. A Spearman's rho correlation coefficient was used to check the correlation among POP scores serum AChE level, length of hospital stay (LOS), amount of atropine and pralidoxime used.

A Mann-Whitney U test was used to determine any differences between two groups. A *P* value of less than 0.05 or less was considered to be statistically significant.

Results

A total number of 100 cases were enrolled in the study. The mean age of the patient was 30 ± 14.3 SD with female male ratio of 1.22: 1. The median value (Q1, Q3) of serum AChE was 2219.5 IU/L (832.7, 5005.7). The median value (Q1, Q3) of POP score was 3. (2, 4). In this

study, out of 100 patients, 57 (57%) were classified as mild, 38 (38%) moderate and 5 (5%) as severe poisoning (Table1).

Table 1: Characteristics of patients with OP poisoning (n= 100)

Patients status	Description
Age (years)	30 ± 14.3
Female Male	55% 45%
Female : Male	1.22
Serum AChE level (Q1, Q3)	2219.5 IU/L (832.7- 5005)
POP score 0 - 3 mild 4 - 7 moderate 8 - 11 severe	 57 38 5
Atropine used (Q1, Q3) 1 ampoule = 0.6 mg	20 (5, 50)= 12 mg
Hospital stay in days (Q1, Q3)	4 (1 - 6)

The mortality rate recorded was 4%. Twenty-two (22%) of patients were left against medical advice (LAMA), were referred or discharged on personal request (DOPR). The further analysis included only 78% patients which we were able to follow up (Table 2).

Table 2: Comparison of characteristics of patients with OP poisoning (n= 78)

Patients status	Deaths (n= 4)	Survivors (n= 74)	*P*
Age (years)	28 ± 11.35	28.7 ± 13.13	0.001
Level of education: No School Primary School High School Intermediate Level Bachelor Level	 0 3 1 0 0	 16 12 41 2 3	0.072
Occupation: Student Homemaker Farmer Workers	 1 1 2 0	 14 30 21 9	0.707
POP Score	4 (Q1, Q3, 4, 7.75)	3 (Q1, Q3, 2, 4)	0.045
Serum AChE level (IU/L)	588 (Q1, Q3,173, 1912)	2221 (Q1, Q3, 768.5, 4703.5)	0.088
Length of hospital stay in days	3.5 (Q1, Q3, 1, 11.25)	5 (Q1, Q3, 3, 7)	0.623
Atropine used (1 amp= 0.6mg)	170 (Q1, Q3, 152.5, 297) = 102 mg	15 (Q1,Q3, 8.75, 34.75)= 9mg	0.0001

The median (Q1, Q3) POP score was 4 (Q1, Q3, 4, 7.75) in mortality group and the median (Q1, Q3) POP score was 3 (Q1, Q3, 2, 4) in non-mortality group, *P*= 0.045. Similarly, the median (Q1, Q3) serum AChE level was 588 (Q1, Q3, 173, 1912) in mortality group and the median (Q1, Q3) serum AChE was 2221 (Q1, Q3, 768.5, 4703.5) in non-mortality group, *P* = 0.088. The median (Q1, Q3) atropine used was 170 ampoules (Q1, Q3, 152.5, 297) = 102 mg (1

ampoule of atropine = 0.6 mg) in mortality group and the median (Q1, Q3) atropine used was 15 (Q1, Q3, 8.75, 34.75) = 9 mg in survivor group, *P* = 0.0001. Seventy four (74%) survived patients were brought at (4.1± 2.9; 95% CI, 3.43- 4.80; *P*= 0.001) whereas, 4% of patient who died were brought at (7.5 ± 5.4; 95% CI, 10.18- 46.31; *P*= 0.001) hours in emergency ward after the consumption of OP compound as stated by patients him/herself or their relatives. Significant statistical difference was found in terms of serum AChE level, atropine used between non-survivor and survivor group (Figure 1).

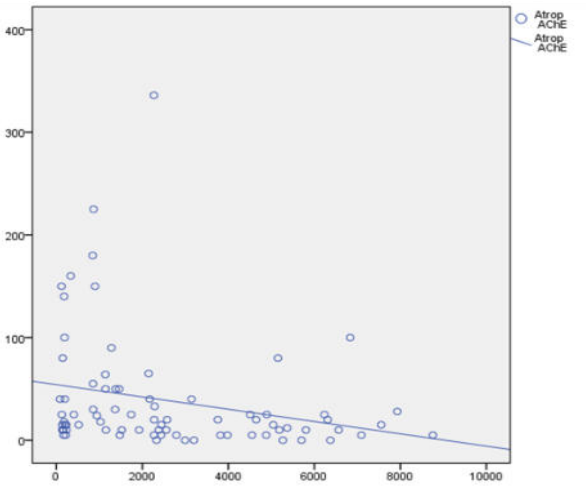

Figure 1: Scatter diagram showing linear correlation between Serum AChE and Atropine used. X-Axis showing atropine used in ampoules while Y-axis showing serum AChE level in IU/L.

A Spearman's rho correlation coefficients test was performed and it showed significant correlation between POP score, serum AChE, atropine used and length of hospital stay (LOS) as shown in Table 3.

Table 3: Correlation between different parameters of OP poisoned patients

Correlation between different parameters of OP poisoned patients (n= 78)		
Parameters	**Spearman's rho correlation coefficient**	***P***
POP score and serum AChE	-0.356	0.001
Serum AChE and Atropine	-0.344	0.005
POP score and Atropine	0.536	0.001

Discussion

More than two thirds of the patients were younger (30 ± 10.3 years) and there was a female preponderance (55% vs. 45%) which are consistent with other studies[19,20] except one study where male outnumbered the females (57% vs. 43%) with all kind of pesticides[21].

This study observed that survivors versus non-survivors were homemakers (30 vs.1), farmers (21 vs. 2), students (14 vs. 1) who were primary schoolers and were unaware of the lethality of OP compounds. Majority of the patients were from agricultural background where these insecticides are widely used and are easily available. Unemployment, poverty and conflicting relationships in young couples might explain the reason for higher incidence of OP poisoning among married couples in comparison to the unmarried (70/100% versus 30/100%) which are consistent with other study.[22,23]

Serum AChE level must be interpreted carefully on admission because many of the cases (61%) with mild to moderate OP poisoning had serum AChE level inhibited to less than 3167 IU/L. The signs and symptoms of OP poisoning only appear above 50% serum AChE inhibition and death occurs at 90% AChE inhibition if adequate treatment is not provided. Clinical

severity has been graded on the basis of the serum AChE level (mild 20-50% enzyme activity, moderate 10-20% enzyme activity and severe <10% enzyme activity).[17,23]

In contrast, serum AChE was not inhibited in 35% of patients with OP poisoning which was similar to study done by M. Eddleston et al.[24] Study done by Bhattarai et al reported that the level of cholinesterase activity does not all the time correlate with clinical illness.[22] Small short-term exposures can depress cholinesterase activity to very low levels with minimal symptoms. Nevertheless, plasma AChE level on admission was useful for most of the patients who survived from the best cut-off values chosen.

The present study found that POP score of 3 or less (mild poisoning) patients with serum AChE level ≤ 2221IU/L survived because they reached hospital and resuscitated in time with median LOS of 5 days. In contrast, with POP score of ≥ 4 (moderate poisoning) patients with serum AChE level ≤ 588 IU/L on admission died with median LOS of 3.5 days because they did not reach hospital in time which is comparable to other study.[25]

Study limitations

The present study had some limitations. The study was carried out in a single tertiary hospital setting. Though the level of hospital, clinical features of poisoning, time of arrival to emergency are mentioned in the study, other variables such as amount of toxins, age of toxins could be the potential confounders in their effective outcome. The study may not represent the total population of the country as only 100 cases were enrolled in the study. In addition, the data for analysis were non parametrical, hence, Spearman's rank correlation coefficient or Spearman's rho was used for analysis.

Recommendation

Further research is necessary to determine the validity of these results. However, these results challenge the treating physicians in a setting of significantly constrained facilities. The recommendation is that a proper local hospital-based protocol should be made for the prompt identification of severity of organophosphate poisoning so that morbidity and mortality could be minimized in future endeavors. Government agencies and non-government health organizations should take a lead locally in this initiative towards the management of pesticide poisoning.

Conclusions

The present study revealed significant correlation between POP score, serum AChE level, atropine used and length of hospital stay (LOS). Serum AChE level on admission can provide useful information but it must be interpreted carefully with POP score.

The variation from time and amount of ingestion to admission may be the factor obscuring relationship between POP score and serum AChE level. However, serum AChE level will always be required as a helpful approach to predict the outcome of patients.

List of abbreviations

AChE: Acetylcholinesterase
ICU: Intensive Care Unit
LAMA: Left against medical advice
DOPR: Discharged on Personal Request
OP: Organophosphate
POP: Peradeniya Organophosphorus Poisoning
PAM: Pralidoxime
SD: Standard Deviation

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Competing interests:

The authors declare that they have no competing interests.

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Additional file 1: Peradeniya Organophosphorus Poisoning (POP) Scale

Parameter	Clinical criteria	Score
Pupil Size	> 2 mm	0
	< 2 mm	1
	Pin-point	2
Respiratory rate	< 20/min	0
	> 20/min	1
	> 20/min with central cyanosis	2

Heart rate	> 60/min	0
	41- 60/min	1
	< 40/min	2
Fasciculation	None	0
	Present, generalized or 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
	Total Observed Score	

Observed POP score:

0-3: Mild poisoning (___) 4-7: Moderate poisoning (___) 8-11: Severe poisoning (___)

Additional file 2. Correlation of biochemical parameters with plasma cholinesterase

Parameters	Serum acetylcholinesterase level	P- value
	Spearman's correlation coefficient	
POP scale		

Outcome:

Survived/ Expired/ Referred/ LAMA

Atropine: Ampoules, (mg): ____ampoules.

Pralidoxime: Ampoules, (mg): ____ampoules

Duration of Emergency stay: ____ days.