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ORIGINAL ARTICLE

Leukocyte Count: A Reliable Marker for Severity of Organophosphorus Intoxication

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ABSTRACT

Introduction: To determine reliability of leukocyte count on admission for prediction of mortality among patients with organophosphorus intoxication. Early prediction can help in preventing the poor outcome and improved management. This is cost and time effective method and better management and preventive protocols can be developed.

Objective: To determine the diagnostic accuracy of leukocyte count in prediction of mortality in patients with organophosphorus intoxication keeping actual mortality as gold standard.

Material and Methods: The design of this study was a Cross sectional study design. The duration of this study was six months from 31-03-2020 to 30-09-2020 and this study was conducted in the Department of Medicine (unit II), HFH, Rawalpindi. A total of one hundred and sixty (n=160) patients of either gender between age between 16-85 years who were confirmed cases of organophosphorus poisoning were enrolled. Leukocyte count levels were noted at the time of admission and patients were monitored for 7 days in the hospital for mortality.

Results: The results showed that sensitivity, specificity, positive predictive value, negative predictive value and accuracy of raised leukocytes counts (>12000/uL) at admission as 60.4%, 77.8%, 50.0%, 84.3% and 73.1% respectively. ROC curve showed best cutoff value of raised leukocytes counts (>12000/uL) at admission as 10253/uL, where sensitivity of 72.1% and specificity of 58.1% was achieved. Area under the curve (AUC) was calculated as 0.707.

Practical Implication: To determine the diagnostic accuracy of leukocyte count in prediction of mortality in patients with organophosphorus intoxication keeping actual mortality as gold standard

Conclusions: Raised leukocytes counts (>12000/uL) at admission allowed prediction of mortality in patients with organophosphorus poisoning with reasonable accuracy. Our study results showed sensitivity, specificity, PPV, NPV and accuracy of 60.4%, 77.8%, 50.0%, 84.3% and 73.1% respectively.

Keywords: Leukocyte Counts, Organophosphorus, Poisoning, Mortality, Intoxication, Predictive Value, Morbidity.

INTRODUCTION

Organophosphorus compounds are a heterogeneous group of insecticides widely used in agricultural industry. These organophosphorus compounds are likely to have more adverse effects in developing countries like India due to its easy availability and less awareness which results in high morbidity and mortality [1]. The frequency of poor outcome (mortality) is 43% in patients with organophosphate intoxication [2]. Acute organophosphate poisoning is a major health problem in developing countries and is also responsible for many deaths in the world annually [3]. Because of the high mortality and morbidity of acute organophosphate poisoning, rapid diagnosis and treatment is often necessary [(4)]. Establishing the relevant prognostic factors in the clinical setting is crucial for the management of patients with acute organophosphate poisoning [5,6,7]. Leukocytosis in stress like injury, poisoning is due to neutrophilia caused by neutrophil margination, and not due to increased marrow production. Normally, they are produced in the bone marrow and comprise approximately 60% of the blood. These cells are critically important to an immune response and migrate from the blood to tissues during an infection and stress-like poisoning. Theoretically, patients with significant stress should have a higher degree of leukocytosis compared to patients with minor stress [2].

Since the complete blood count is one of the most common tests obtained in Intensive Care Unit (ICU) patients, leukocytes level could serve as an easy-to-obtain marker for severity of organophosphorus poisoning (OPP). In centers where the measurement of cholinesterase activity cannot be done, management is based on the assessment of severity of intoxication, which depends largely on clinical findings and basic blood parameters such as leukocyte count. Leukocytosis is a common finding in organophosphate intoxication [(8)]. Monitoring of the leukocyte number in conjunction with clinical signs may be helpful in assessment of the prognosis and efficacy of treatment in centers where the measurement of cholinesterase activity cannot be done [(8,9)]. Leukocyte count had a sensitivity of 60%, specificity of 76%, and negative predictive value of 85% if counts were >12,000 in prediction of mortality in patients with organophosphate intoxication [(10)]. Rationale of this study is to determine whether the monitoring of number of leucocytes may be taken as a marker for the severity of organophosphorus intoxication. Early prediction of prognosis can help in preventing the poor outcome and improved management. This is cost and time effective method but less data found in this regard, moreover, local data is also missing [(11)]. So, we planned to conduct this study to determine whether leukocyte count is reliable for prediction of the mortality of organophosphorus intoxication, so that better management and preventive protocols can be developed.

MATERIALS AND METHODS

Study Design: Cross sectional validation study

Setting: Department of Medicine (unit II), Holy Family Hospital, Rawalpindi

Duration: Six months (31-03-2020 to 30-09-2020)

Sample Size: Sample size of 160 cases is calculated with 95% confidence level, taking expected percentage of mortality i.e. 43% and sensitivity of leukocyte count i.e. 60% with 10% margin of error and specificity i.e. 76% with 10% margin of error

Sampling Technique: Non-probability consecutive.

Inclusion Criteria: Patients of age 16-85 years of either gender presenting with intake of organophosphorus poisoning

Exclusion Criteria:

1 Patients presented with recurrent intake of organophosphorus poisoning.

2 Patients with double insecticide/multiple poisoning with other drugs like opioids, diazepam, and alcohol.

Data Collection Procedure: A total of 160 patients fulfilling the selection criteria were included in this study from Emergency

Department of Medicine, Holy Family Hospital, Rawalpindi. Informed consent was obtained from attendants. Demographic information including name, age, gender, duration of organophosphorus poisoning, intention (suicidal/homicidal) was also noted. Then blood sample was obtained by using 5cc disposable syringe. All samples were stored in sterile vials and sent to the laboratory of the hospital for assessment of leukocyte count. Reports were assessed and leukocyte count levels were noted. Patients were labeled as positive or negative (as per operational definition). Then patients were followed-up in wards for 7 days. Within 7 days of hospital stay, if patients died, then mortality was confirmed (as per operational definition). All this information was recorded on proforma (attached).

Data Analysis Procedure: Data was entered and analyzed through in SPSS version 20. Quantitative variables like age and duration of organophosphorus poisoning were presented as mean and standard deviation. Qualitative variables like gender, occupation, intention, literacy status and mortality (on leukocyte count and mortality occurred) were presented as frequency and percentage. A 2x2 table was generated to calculate sensitivity, specificity, PPV, NPV and diagnostic accuracy of leukocyte count. Data was stratified for age, gender, occupation, intention, literacy status and duration of organophosphorus poisoning. Poststratification, 2x2 tables was generated to calculate sensitivity, specificity, PPV, NPV and diagnostic accuracy of leukocyte count was calculated. ROC on likelihood ratios were also calculated.

Table 1:

		Mortality	
		Positive	Negative
Leukocyte count >12,000	Positive	TP	FP
	Negative	FN	TN

$$\text{Sensitivity} = \frac{TP}{TP+FN} \times 100$$

$$\text{Specificity} = \frac{TN}{TN+FP} \times 100$$

$$\text{Positive predictive value} = \frac{TP}{TP+FP} \times 100$$

$$\text{Negative predictive value} = \frac{TN}{FN+TN} \times 100$$

RESULTS

A total of one hundred and sixty (n=160) patients of either gender between age between 16-85 years who were confirmed cases of organophosphorus poisoning were enrolled in the study. Leukocyte count levels were noted at the time of admission and patients were monitored for 7 days in the hospital for mortality. Gender and age distribution shown in 2 and Table 3, respectively. Mean duration and different duration groups in the study sample are presented in Table 4. Education status and reason of poison intake mentioned in table 5. Results of leukocyte count analysis and clinical follow up are presented in table 6 and 7 respectively. There were 32.5% (n=52/160) of patients who had their leukocytes counts >12000/uL and 67.5% (n=108/160) had leukocytes counts ≤ 12000/uL (table 6). Mortality occurred in 26.9% (n=43/160) of patients on clinical follow up till day 7 (Table 7). Both the results were cross tabulated (table 8). A total of 16.3% (n=26/160) of patients were true positives, 56.9% (n=91/160) were true negatives, 16.3% (n=26/160) were false positives and 10.5% (n=17/160) were false negatives (table 8). We calculated five parameters: sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy for the validation purpose. Our study results showed that sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 60.4%, 77.8%, 50.0%, 84.3% and 73.1% respectively (Table 8).

Table 2: Gender Distribution

Gender	Frequency	Percent
Males	102	63.8
Females	58	36.3
Total	160	100.0

Table 3: Age Distribution in Study Sample

Age Groups	n (%)	Mean Age (Years)	Std. Dev
≤40 YEARS	106 (66.3%)	26.7	6.3
>40 YEARS	54 (33.8%)	47.6	7.2
TOTAL	160 (100%)	33.7	11.9

Table 4: Duration of Poisoning in Study Sample

Duration Groups	n (%)	Mean Duration (Hours)	Std. Dev
≤6 HOURS	93 (58.1%)	5.1	0.92
> 6 HOURS	67 (41.9%)	8.1	1.2
TOTAL	160 (100%)	6.3	1.9

Table 5: Education and Intention Status Distribution

Variables		Frequency	Percent
Education	Educated	102	63.8
	Illiterate	58	36.3
	Total	160	100.0
Intention	Suicidal	160	100
	Homicidal	0	0
	Total	160	100.0

Table 6: Leukocyte Counts in Study Sample

Leukocyte Counts	n (%)	Mean Leukocyte Counts (Per Ul)	Std. Dev
>12000	52 (32.5%)	12840.7	577.9
≤ 12000	108 (67.5%)	9521.9	8883.6
Total	160 (100%)	10600.5	7459.7

Table 7: Death During 7 Days

Patient Death	Frequency	Percent
Positive	43	26.9
Negative	117	73.1
Total	160	100.0

Table 8: Cross Tabulation Between Leukocyte Counts and Death of Patients

Leukocyte Counts	Patient Death		Total	Accuracy
	Positive	Negative		
>12000	26	26	52	Sensitivity: 60.4%
≤ 12000				Specificity: 77.8%
Total	17	91	108	PPV: 50.0%
	43	117	160	NPV: 84.3% Accuracy: 73.1% +LR: 2.7

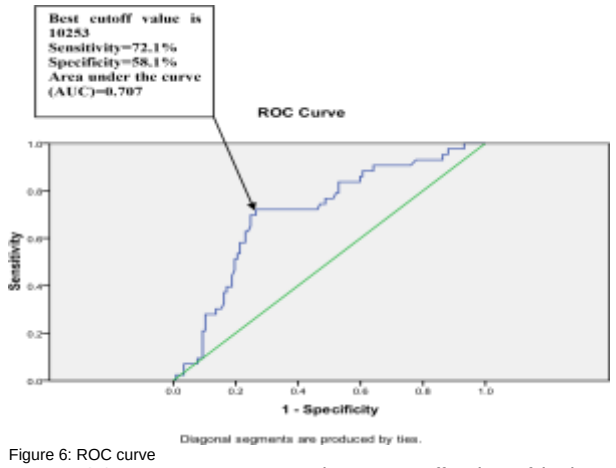

Figure 6: ROC curve

ROC curve was generated. Best cutoff value of leukocytes counts came out to be 10253/uL (left upper corner of the curve as shown in figure 6), where sensitivity of 72.1% and specificity of 58.1% was achieved. Area under the curve (AUC) was calculated as 0.707 (figure 6). Similar trends (relatively lower sensitivity and high specificity) in the predictive accuracy of leukocyte counts at admission were noted when data was stratified with respect to age (table 9), gender (table 10), duration of poisoning.

(Table 11) and education status (table 12).

Table 9: Cross Tabulation Between Leukocyte Counts and Death of Patients (Stratification W.R.T Age)

Age Groups	Leukocyte Counts	Patient Death		Total	Accuracy
		Positive	Negative		
≤40 Years	>12000	17	21	38 68	Sensitivity: 65.4% Specificity: 73.8% PPV: 44.7% NPV: 86.8% Accuracy: 71.7% +LR: 2.5
	≤ 12000	9	59		
≤40 Years	>12000	9	5	14 40	Sensitivity: 52.9% Specificity: 86.5% PPV: 64.3% NPV: 80.0% Accuracy: 75.9% +LR: 3.9
	≤ 12000	8	32		

Table 10: Cross Tabulation Between Leukocyte Counts and Death Of Patients (Stratification W.R.T Gender)

Gender	Leukocyte Counts	Patient Death		Total	Accuracy
		Positive	Negative		
Males	>12000	20	15	35 67	Sensitivity: 66.7% Specificity: 79.2% PPV: 57.1% NPV: 85.1% Accuracy: 75.5% +LR: 3.2
	≤ 12000	10	57		
Females	>12000	6	11	17 41	Sensitivity: 46.2% Specificity: 75.6% PPV: 35.3% NPV: 82.9% Accuracy: 68.9% +LR: 1.9
	≤ 12000	7	34		

Table 11: Cross Tabulation Between Leukocyte Counts and Death of Patients (Stratification W.R.T Duration of Poisoning)

Duration Groups	Leukocyte Counts	Patient Death		Total	Accuracy
		Positive	Negative		
≤6 Hours	>12000	14	13	27	Sensitivity: 56.0% Specificity: 80.1% PPV: 51.9% NPV: 83.3% Accuracy: 74.2% +LR: 297
	≤ 12000	11	55	66	
>6 Hours	>12000	12	13	25	Sensitivity: 52.1% Specificity: 73.5%
	≤ 12000	6	36	42	PPV: 48.0% NPV: 76.6% Accuracy: 66.7% +LR: 1.9

Table 12: Cross Tabulation Between Leukocyte Counts and Death of Patients (Stratification W.R.T Education Status)

Education Status	Leukocyte Counts	Patient Death		Total	Accuracy
		Positive	Negative		
Educated	>12000	17	17	34 66	Sensitivity: 60.7% Specificity: 76.4% PPV: 50.0% NPV: 83.3% Accuracy: 72.0% +LR: 2.6
	≤ 12000	11	55		
Illiterate	>12000	9	9	18 42	Sensitivity: 60.0% Specificity: 80.0% PPV: 50.0% NPV: 85.7% Accuracy: 75.0% +LR: 3.0
	≤ 12000	6	36		

DISCUSSION

Organophosphates (OP) are frequently used as pesticides around the world in agriculture. Organophosphorus pesticides related self-harm is a fairly common clinical entity responsible for over two thirds of pesticide related deaths in the rural areas of developing countries Acute toxicity manifests as cholinergic crisis with glandular secretions, myasthenic-like syndrome [12,13], peripheral neuropathies, neuropsychiatric abnormalities, extrapyramidal disorders, altered mental status, and weakness. Several studies suggest that there are hematological alterations in these patients that could possibly be associated with prognosis [14]. Present study was planned to determine reliability of leukocyte count on admission for prediction of mortality among patients with organophosphorus intoxication. Early prediction can help in preventing the poor outcome and improved management [15-18]. A total of one hundred and sixty (n=160) patients of either gender between age between 16-85 years who were confirmed cases of organophosphorus poisoning (OPP) were enrolled. Leukocyte count levels were noted at the time of admission and patients were monitored for 7 days in the hospital for mortality [19].

Our study results showed that sensitivity, specificity, positive predictive value, negative predictive value and accuracy of raised leukocytes counts (>12000/uL) at admission as 60.4%, 77.8%, 50.0%, 84.3% and 73.1% respectively [20]. ROC curve showed best cutoff value of raised leukocytes counts (>12000/uL) at admission as 10253/uL, where sensitivity of 72.1% and specificity of 58.1% was achieved. Area under the curve (AUC) was calculated as 0.707. Our results are comparable with already published data on the subject. Kumar S et al in their prospective study aimed to correlate the severity of acute OPP with leukocyte count and also to assess the prognosis [21]. They enrolled 80 patients suspected of OPP of age >15 years admitted to emergency. Serum cholinesterase level and leukocyte count were estimated at the time of admission in all patients and severity of OPP was assessed according to Peradeniya organophosphorus poisoning (POP) scale [22,23]. Their results showed that the severity of poisoning was directly correlated with serum cholinesterase level (P= 0.0001). Raised leukocyte count (>12000/uL) had a sensitivity of 60%, specificity of 76%, and negative predictive value of 85%. The specificity and was improved when cutoff for leukocyte counts was taken as >15000/uL [10]. In the present study raised we found similar results with raised leukocytes counts (>1200/uL). We, however, did not include other parameters like serum cholinesterase level as our outcome variables. Tang Y et determined the diagnostic value of the CBC in organophosphorus poisoning. A total of 90 OPPs poisoning patients were included and compared with age matched health controls. Their results showed that both white blood cell (WBC) and neutrophils (NE) counts showed statistical differences between the severe poisoning group and the moderate poisoning group [11]. Their results showed that both white blood cell (WBC) and neutrophils

(NE) counts were the most important indexes in PQ- and OPPs-poisoned patients. In OPPs poisoning patients, WBC and NE showed statistical differences between the severe poisoning group and the moderate poisoning group. Their areas under the ROC curve (AUC) were 0.673 (WBC) and 0.669 (NE), which were higher than cholinesterase (CHE; AUC 0.326). They concluded that the CBC indices had a diagnostic value in PQ and OPPs poisoning; WBC and NE were the first responses and had clinical significance in PQ and OPPs poisoning; moreover, they are better than CHE in diagnosing OPPs poisoning [24].

Amanvermez R et al evaluated the relationship between laboratory parameters and the degree of intoxication in patients attempted to suicide using organophosphate admitted to the emergency department. Ninety-one patients who attempted to suicide with acute organophosphate poisoning admitted to the emergency service were included. Their results showed that leukocyte counts, glucose and amylase levels were significantly higher in the grade 1 and 2, but they were considerably elevated in the grade 3 compared to normal reference [25]. Hundekari IA et al assessed the oxidative damage, hemoglobin level and leukocyte count in acute organophosphorus pesticide poisoning. Their results showed that Leucocytosis was observed in these cases signifies the activation of defense mechanism which could be a positive response for survival [16]. Dündar ZD et al showed that severe poisoning cases on mechanical ventilation had significantly higher leukocyte counts than non-ventilated patients (p=0.004 respectively). Dong N et al designed a study to establish a scoring system to assess the risk of cases with severe OPP. A risk score for patients with severe OPP was developed. The rates of severe AOPP cases were 20.7% and 20.1% in the derivation and validation cohorts, respectively. A scoring system for severe AOPP risk was developed that included white blood cell count of >15 × 10^9/L along with other parameters like age >50 years, plasma cholinesterase of <360 U/L, plasma albumin of <35 g/L, blood pH <7.3, and lactic acid >3.0 mmol/L. In the present study raised leukocytes counts (>1200/uL) was associated with higher rates of mortality. We, however, did not include other parameters as our outcome variables [5].

Other investigators have explored other hematological parameters that could have prognostic value in OPP patients. Dündar ZD et al investigated the prognostic value of red cell distribution width (RDW) measured on admission to the emergency department in patients with organophosphate poisoning. Their results showed that severe poisoning cases on mechanical ventilation had significantly higher RDW levels than non-ventilated patients (p<0.001). The area under the receiver-operating characteristic curve of RDW levels for predicting mechanical ventilation requirement was 0.716 (95% CI: 0.581-0.852, p=0.010). RDW had a sensitivity of 73%, specificity of 70%, and negative predictive value of 91% with a cut-off value of 14.5% in predicting mechanical ventilation requirement in patients with organophosphate poisoning [26].

In our study results and the cumulative evidence on the subject demonstrates that leukocytosis is frequently observed in patients suspected of OPP and is associated with severity of disease and poor prognosis. Higher specificity and negative predictive value of leukocytosis renders it as a reliable predictor of poor outcomes. It is non-invasive, cost-effective, and readily available. One can reliably triage the high-risk patients with this simple test at the time of admission. A prospective design of the present study is its major strength. There are several limitations to our study. Firstly, we feel the sample size is relatively smaller but sufficient to draw the inference. The other limitation is we only used single parameter with single cutoff value. We suggest future studies with larger sample size and taking into considerations different cutoff values and other parameters like RDW. Combination of different parameters may be more predictive of poor outcomes.

CONCLUSIONS

In the present study, raised leukocytes counts (>12000/uL) at admission allowed prediction of mortality in patients with organophosphorus poisoning with reasonable accuracy. Our study results showed sensitivity, specificity, PPV, NPV and accuracy of 60.4%, 77.8%, 50.0%, 84.3% and 73.1% respectively. We suggest future studies with larger sample size and taking into considerations different cutoff values and other parameters like RDW. Combination of different parameters may be more predictive of poor outcomes.

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