Original Article

Impact Of Chronic Exposure Of Organophosphorus Pesticide On Hematological And Biochemical Parameters Of Agriculture Workers: A Cross Sectional Study

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Abstract

Background:

The uncontrolled long-term exposure to organophosphorus pesticides is harmful to health especially in agricultural workers.

Objective:

This study was designed to assess hematological and biochemical parameters of agricultural workers occupationally exposed to organophosphorus pesticides.

Methodology:

A cross sectional study was conducted at Baqai Medical University, Muhammadi blood bank & diagnostic center, Karachi. Samples were collected from 193 pesticide sprayers (aged 20-59 years) working for ≥ 2 years in agriculture farms, located in district Mirpurkhas, Sindh, Pakistan. A comparison was made by equal numbers of controls living in same vicinity but not involved in spraying pesticide. Complete blood count was determined on Sysmex Xp 100 automated hematology analyzer by Tokyo, Japan. Serum cholinesterase (ChE), as a biomarker of chronic organophosphorus pesticide exposure, was measured on Cobas c 311 clinical chemistry analyzer by Roche Diagnostics International Ltd and Liver function tests were performed on Cobas c111 chemistry analyzer, Germany.

Results:

Serum ChE level of exposed group was significantly lower than non-exposed ($p < .001$). 49.7% individuals in exposed group had serum ChE levels below the reference value. The hematological parameters especially Hb, RBC, MCV, MCH, MCHC, WBC, neutrophils, lymphocyte, and platelet counts were significantly altered in exposed group than non-exposed group. Hemoglobin concentration was significantly reduced in exposed group as compared to non-exposed group ($p < 0.001$). There was significant relationship between exposure of pesticide and degree of anemia; exposed group was more likely to develop anemia than non-exposed group ($p < 0.001$). In biochemical parameters serum alkaline phosphatase (ALP) and serum aspartate aminotransferase (AST) of exposed group was significantly high as compared to non-exposed group ($p < 0.001$).

Conclusion:

Long-term exposure to cholinesterase-inhibiting agricultural pesticides is associated with alterations in hematological parameters along with deranged liver function tests.

Keywords: organophosphorus pesticides, hematological parameters, biochemical parameters, agriculture workers

INTRODUCTION:

Pakistan's agriculture sector plays a central role in the economy of the country [1]. Population growth alongside increased demand of food production placing pressure on agriculture. To increase per acer yield world is adapting more efficient methods for cultivation but still facing hazards of pesticides exposure [2]. Occupational pesticide toxicity encompasses a large group of population, residing mostly in developing countries, where a substantial proportion of the active population is involved in agriculture and pesticide application in unsuitable conditions, including the usage of limited compounds and inappropriate spraying equipments [3]. Many experimental, epidemiological studies, and clinical researches proved pesticides as a potential health hazard to human especially occupationally involved agriculture workers. [2]. The organophosphate pesticides (OP) are used worldwide due to broad spectrum, highly effective mode of action and more toxicity to pests [4]. OP compounds are anti-acetylcholinesterase which intensifies their toxicity by permitting neurotransmitter acetylcholine (ACh) to overact at its receptors in the central and peripheral nervous system [5]. The anticholinesterase effects can be demonstrated biochemically by decreased levels of serum pseudocholinesterase (PCE) and red cell cholinesterase. Acetylcholinesterase is an enzyme that breaks down the acetylcholine (ACh) into choline and acetic acid [6]. Pseudo cholinesterase, which is a liver acute phase protein found in plasma and nervous tissue, is blocked by organophosphorus compounds in a similar fashion to acetylcholinesterase. Organophosphates inhibit acetylcholinesterase by phosphorylating the serine hydroxyl group present at the active site of acetylcholinesterase [7]. Cholinesterase commonly used as biomarker of acute or chronic exposure to OP pesticides [8]. Moreover, it has been reported that serum ChE activity is somewhat more sensitive indicator of mixed pesticide exposure as compared to red blood cell acetylcholinesterase activity [9].

Unsafe and non-preventive work practices in handling and spraying of pesticides may endanger the agriculture workers to its toxic effects [10]. Occupational exposure to OP compounds exerts various adverse health effects and many studies reported that workers having chronic exposure of OP were more prone to develop neurotoxicity, congenital anomalies, and cancers [11]. Pesticides have been proved to have hematotoxic effects and may trigger aplastic anemia, leucopenia, and thrombopenia to different cytopenias [12]. The chronic OP exposure is linked to many hematological malignancies like, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) [13,14].

Pesticide exposure may produce biochemical alteration even before harmful clinical health effects are revealed especially in agriculture workers. Prolonged exposures to pesticide affect several organs including liver which can be identified by serum enzymes and other biochemical variables among farm workers [15]. The presence of pesticide residues in the blood of agriculture workers were reported in previous studies [16, 17].

Methods and Materials:

It was a cross sectional study conducted at Baqai Medical University and Muhammadi blood bank & diagnostic center, Karachi. The samples were collected from agricultural workers residing in district Mirpurkhas, Sindh. The study was approved by the ethics committee of Baqai Medical University, Karachi. In total 386 subjects were included in this study of which one hundred ninety-three males, aged 20 to 59 years, were agriculture workers and occupationally exposed to organophosphorus pesticide for ≥2years. The study was compared with equal number of healthy males having no previous or current occupational exposure to pesticides taken as controls from nearby area. The individuals with a history of acute or chronic illness, like liver, renal, cardiovascular disease and age < 20 and > 59 years were excluded. Written informed consent was taken from all the participants after explaining details of study procedure. For assessment of health status, a detailed personal history and medical history was taken which also included the comprehensive information about the use of pesticide i.e., the kind of pesticide, technique of spraying the pesticides, information about the handling of the pesticides and use of any post spraying precautionary measures. A brief general physical examination was done including blood pressure, temperature, pulse, height, weight of all participants. 10 ml venous blood samples were collected. Purple top (EDTA) and yellow top (gel containing) vacutainers were labeled with the participants identification. Equal amount of blood was transferred into both vacutainers. Serum specimens for Cholinesterase (ChE) were collected in yellow top vacutainers containing separating gel. Specimen kept cold and protected from light. All specimens were transported on dry ice to the laboratory. Serum was separated by centrifugation (2000 rpm for 10 mins) and transferred to aliquots, stored at < -20 ℃ within 1 hour of collection. Whole blood samples were kept at 4℃ and analyzed within 2 hours of sampling. Serum cholinesterase enzyme (ChE) level was measured on Cobas c 311 clinical chemistry analyzer by Roche Diagnostics International Ltd and LFTs were performed on Cobas c111 chemistry analyzer, Germany. Complete blood count was done on Sysmex Xp 100 automated hematology analyzer manufactured by Tokyo, Japan. The data was tabulated on Microsoft excel. Statistical analysis was done by using SPSS version 25.0. Descriptive statistics have been applied for the demographic parameters in the exposed and un exposed groups. All the categorical parameters were elaborated by frequencies and percentages. Student's t test was used to compare the mean values of the quantitative characteristics between the exposed and non-exposed group. For comparison of the categorical outcomes Chi square test was applied. The level of significance was kept at p<0.05.

Results:

Table 1 displayed the physical features, personal habits and exposure periods of study subjects. The mean ages (years) of exposed group and non -exposed group were 38.7± 10.75 and 38.5± 9.45. There was no significant difference in age, height, weight and BMI. Mean pesticide exposure among sprayers was found to be 11.23±8.68 years.

Table 1. Baseline characteristics of study population

Parameters	Exposed group(N=193)	Non exposed group(N=193)
Age(yrs) [Mean ± SD]	38.73±10.75	38.58±9.45
Height (cm) [Mean ± SD]	171±5.67	170±8.98
Weight (Kg) [Mean ± SD]	65±14.45	64.78±13.76
BMI(Kg/m^2)	21.56±5.67	20.96±4.59
Smoker n (%)	22(11.39)*	15(7.77)*
Duration of pesticide exposure (yrs) [Mean ± SD]	11.23±8.68	0.00±0.0
Education level n (%)		
Illiterate	90(46.63)	85(44.04)
Primary	50(25.90)	89(46.11)
Secondary	29(15.02)	11(5.69)
Higher	24(12.43)	8(4.14)

N= number of participants; % frequency; Student's t-test,*p<.001

Cholinesterase level: Cholinesterase was taken as biomarker of organophosphate pesticides exposure and levels were compared between exposed and non-exposed groups as shown in Table 2. The levels of serum cholinesterase was significantly reduced in exposed subjects as compared to un exposed subjects (p<.001). There was a significant difference in number of individuals having serum cholinesterase levels below the normal range between exposed and un exposed group (p<.001). It was more likely that exposed individuals had serum cholinesterase below the normal range than non-exposed group (OR- 9.487; 95% CI- 2.87–15.67).

Table 2. Serum ChE levels of exposed group and Non exposed group

Cholinesterase Levels	Exposed group (N=193)	Non-Exposed group (N=193)	P value
Reference range (U/L) [4620-11500]	3830±1500	10058±900	<.001*

Individuals below the reference range	96 (49.74%)	4(2.07%)	<.001**

N= Number of study subjects; %= Percentage of study subjects; ChE= cholinesterase enzyme; *As per student t-test significant value; **Chi square test.

Hematological findings: There was a significant difference in Hb (p<0.001), RBC(p<0.001), Hct (p=0.01) levels of exposed and non-exposed groups as shown in Table 3. Similarly, we found a significant difference in MCH (p=0.013), MCV (p=0.01), MCHC (p<0.001) between exposed and unexposed groups. The mean MCH, was 26.44 Pg (SD±1.84), and 29.81 Pg (SD±3.89) p-value 0.013 of exposed and non-exposed groups, respectively. The mean MCV 75.12 fl (SD±4.46), 85.73 fl (SD±2.61), p-value =0.01 of exposed and non-exposed groups, respectively. Moreover, a difference in WBC counts (p<0.001), absolute lymphocyte counts (p<0.001), absolute neutrophil counts (p<0.001) and platelet counts (p=0.01) among both groups was observed (Table 3).

Table 3. Comparison of complete blood count parameters between exposed and non-exposed subjects

Parameters	**Exposed group N= (193)**	**Non exposed group N= (193)**	***P value**
Hb(g/dl)	12.21 ±1.89	14.92±1.34	<0.001
RBC $x10^6$/UL	4.23±0.77	4.63 ±1.66	<0.001
Hct (%)	40.13±0.45	44.34±2.57	0.01
MCH (pg)	26.44 ±1.84	29.81±3.89	0.013
MCHC (%)	28.35±1.97	34.42±1.73	<0.001
MCV (fl)	75.12±4.46	85.73±2.61	0.01
WBC $x10^3$/UL	10.34±3.22	6.12±1.72	<0.001
Lymphocyte $x10^3$/UL	3.98±1.39	1.73±1.43	<0.001
Neutrophil $x10^3$/UL	2.14±2.05	4.06±1.44	<0.001
Platelet $x10^3$/UL	150.84±117.15	251.64±51.92	0.01

*Student's t test was applied; Hb, Hemoglobin; RBC, Red blood cell; Hct, hematocrit; MCH, mean corpuscular Hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; WBC, white blood cell; N= Total number of subjects.

Frequency distribution of hematological variations among study participants were shown in Table 4. Significant (p<0.05) abnormal counts taking both below lower limit and above upper limit from reference range were found for Hb, R.B.C, Hct, MCV, MCH MCHC, W.B.C., neutrophils, lymphocytes, and platelets among exposed group as compared to non-exposed group. In exposed group 63.74% had Hb below normal range, whereas in non-exposed group 10.36% individuals had Hb values below normal range.

Table 4. Frequency distribution of abnormal hematological parameters among exposed and non-exposed group

CBC Parameters	Reference ranges of hematology	Exposed group(N=193) n (%)			Non-exposed group (N=193) n (%)		
		Below lower Limit	Above upper limit	Total	Below lower limit	Above upper limit	Total

RBC	4.02-6.01x10^6/UL	90(46.63)	0(0)	90(46.63)	15(7.77)	10(5.18)	25(12.95)*
Hb	12.4-17.3	121(62.69)	1(0.51)	122(63.20)	20(10.36)	15(7.77)	35(18.13)**
HCT	37.8-50.7(%)	99(51.29)	1(0.51)	100(51.80)	18(9.32)	11(5.69)	29(15.01)**
MCV	80.0-94.9(fl)	109(56.47)	0(0)	109(56.47)	14(7.25)	3(1.55)	17(8.8)*
MCH	27-32(Pg)	99(51.29)	0(0)	99(51.29)	17(8.80)	4(2.07)	21(10.87)**
MCHC	30-35(%)	96(49.74)	0(0)	96(49.74)	19(9.84)	6(3.10)	25(12.94)*
WBC	4.5-9.9x10^3/UL	11(5.6)	85(44.0)	96(49.60)	2(1.03)	1(0.51)	3(1.54)*
Lymphocyte	1.0-3.2X10^3/UL	9(4.66)	75(38.86)	85(43.52)	1(0.51)	0(0.00)	1(0.51)*
Neutrophil	2.4-5.9X10^3/UL	43(22.2)	25(12.95)	68(35.15)	0(0.00)	3(1.55)	3(1.55)*
Platelet	164-343X10^3/UL	65(33.67)	9(4.66)	74(38.33)	1(0.51)	0(0.00)	1(0.51)**

Chi square test was applied; *p<0.001; **p=0.01; CBC, complete blood count; Hb, Hemoglobin; RBC, Red blood cell; Hct, hematocrit; MCH, mean corpuscular Hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; WBC, white blood cell; N= Total number of subjects; n, frequency; %, Percentage.

Categorization of Anemia: Anemic population was categorized into mild, moderate and severe anemia according to World Health Organization guidelines [18]. There was a significant association between category of anemia among exposed and unexposed groups (p<0.001) as shown in Table 5.

Table 5. Categorization of Anemia in exposed and non-exposed groups

Category of Anemia	**Exposed group (N=121)**	**Non-exposed group(N=20)**	***p-value**
	n (%)	**n (%)**	**<0.001**
Mild Anemia (Hb 11.0–12.9 g/dl)	75 (61.98)	12 (60.00)	
Moderate anemia (Hb 8.0–10.9 g/dl)	35(28.92)	5 (25.00)	
Severe anemia (Hb less than 8.0 g/dl)	11 (9.09)	3 (15.00)	

Hb, Hemoglobin; N, number anemic individuals; n, frequency; %, percentage; *As per chi-square

Biochemical parameters: Statistical analysis showed a significant difference in the levels of alkaline phosphatase (ALP) (p<.001) and aspartate aminotransferase (AST) (p<.001) of exposed and unexposed groups. 22.2% and 1.03% of exposed and un exposed groups had AST levels above the reference range, respectively. While, 28.5% and 1.6% of exposed and un exposed groups had Alkaline phosphatase (ALP)levels above the reference range, respectively. No difference in bilirubin direct and indirect levels was observed. Moreover, alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) was found be insignificant among exposed and un exposed groups as shown in Table 6.

Table 6. Comparison LFTs parameters in exposed group & non-exposed groups.

Variables (Reference value)	Exposed group; N=193 Mean (SD)	Non-exposed group; N=193 Mean (SD)	p-value
Alanine aminotransferase (Up to 41U/L)	18.72 (±9.49)	18.70 (±10.81)	0.220*
Bilirubin-Direct (Up to 0.20 mg/dl)	0.19 (±0.10)	0.21 (±0.12)	0.610*
Bilirubin-total (Up to 1.2mg/dl)	0.41 (±0.34)	0.40 (±0.26)	0.077*
Alkaline phosphatase (40-130U/L)	155 ±9.84	56.72 (±17.91)	<.001*
Above ref. value N (%)	55(28.5)	3(1.6)	<.001**
Gamma-glutamyl transferase (<60U/L)	18.91 (±26.47)	16.62 (±18.53)	0.652*
Aspartate aminotransferase (Up to 50U/L)	68.34 (±8.82)	27.49 (±9.88)	<.001*
Above ref. value N (%)	43(22.2)	2(1.03)	<.001**

SD, standard deviation; ref, reference; N, number of study subjects; *As per Student's t test; **As per chi-square; %, percentage

Discussion:

The present study was done to assess alterations in hematological, biochemical parameters, and plasma cholinesterase levels in a specific group of pesticide sprayers occupationally exposed to mixtures of these chemicals for ≥ 2years and to compare these parameters with the non-exposed individuals residing in nearby locality.

The study population was comprised of only male participants. This situation reveals our sociocultural norms and values where only males in rural families have to involve in fields, whereas females are engaged in household work. Moreover, the method of applying pesticides as through knapsack sprayer that was carried on back with about 10 liters of pesticide mixture, operated manually and demanding a lot of physical power. The similar finding was reported by Vikkey et al., in Nigerian farmers where about 94% pesticide spray workers were males [19].

Plasma ChE activity has been used for many years to assess the risk related with pesticide induced toxicity in occupationally exposed workers as well as it is a biomarker of exposure to anticholinesterase pesticides [20]. In the present study plasma cholinesterase was significantly decreased in the exposed group as compared to non-exposed group. 49.7% exposed individuals (96/193) and 2.07% non-exposed individuals (4/193) had serum ChE below the normal range. Our results support the previous findings that reported significant reductions in cholinesterase levels in the pesticide-exposed subjects [21-23]. However, a study conducted in Mexico reported that cholinesterase activity was not significantly reduced in the individuals exposed to a combination of pesticides [24].

The results of this study showed some alterations in the hematological parameters of exposed group as compared to unexposed group. It might be due to OP pesticides exposure which is supported by decreased serum ChE level. RBC, WBC, neutrophils, MCV, MCH, MCHC and platelet count of individuals in exposed group showed significant variations compared to unexposed group. When comparison was done between exposed group (n=193) and non-exposed groups (n=193) on the basis of complete blood count parameters it was observed that 46.6 % (n=90), 62.7% (n=121) and 51.3% (n=99) individuals in exposed group had RBC count, hemoglobin and hematocrit below the reference values, respectively. While thrombocytopenia was observed in 65 individuals (33.7%) in exposed group. Rojas-García et al., reported similar findings[25]. We found a significant association between exposed and non-exposed groups on the basis of categorization of anemia (p<0.001). Out of 121 anemic individuals in exposed group 61.9% (75/121), 28.9% (35/121), 9.1% (11/121) individuals had mild anemia, moderate anemia and severe anemia, respectively. Similar findings were observed in many studies [26-28]**.** Leucocytosis, leucopenia, neutropenia, lymphocytosis were observed mainly in exposed group and had been reported in previous studies [29-32]. Leucocytosis could be an immune defense mechanism against OP chronic poisoning [33,34]. The reduction in RBC count and hemoglobin levels were in line with findings reported by many previous studies, suggesting possible reasons could be the result of the binding of organophosphate pesticides on iron, and impairment in the synthesis of heme and hemoglobin [9].This variation could be result of effect of pesticides on hematopoietic function of bone marrow or a direct toxic effect of pesticides on peripheral blood cells [35-37].Contrary to our study results some studies reported no significant changes in RBC count, hemoglobin, and MCH levels [38-40].

We found a significant difference in serum ALP Levels among exposed and non-exposed groups (p<.001).28.5% individuals in exposed group and 1.6% individuals in un exposed group had ALP levels above the reference range. Moreover, a significant difference was found in serum AST levels between exposed and un exposed group(p<.001). 22.2% exposed individuals and 1.03% unexposed individuals had AST levels above reference value. While no significant difference was noted in ALT, Gamma-glutamyl transferase (GGT) and bilirubin levels. Organophosphorus pesticides alone or in combination may altered liver enzyme functions in occupational workers. Many studies reported abnormal liver function tests especially raised AST, ALT and LDH in agricultural workers [41,42]. This could be toxic effects of pesticides and the existence of pesticide residues in blood [43]. Hernández et al., reported early biochemical alterations in serum enzymes post exposure to combination of pesticides in agricultural workers [44]. Increased activity of ALT and AST were reported in previous studies [45,46]. Yavuz et al., reported that excessive pesticide exposure result in more deranged liver enzymes [47]. Pesticide exposure induces release of cytosolic enzymes from hepatocyte and many other body organs [48]. While Gaikwad, A.S., et al. reported no significant enzymatic activity change in ALP [49].

CONCLUSION

The present study revealed that agricultural workers who were occupational exposed to cholinesterase-inhibiting pesticides for a long period of time, showed altered liver function and hematological abnormalities. The marked decrease of serum cholinesterase in the exposed group along with changes in hematological and LFTs profile recommend monitoring of ChE, complete blood count and LFTs on regular basis to predict and prevent health hazards of OP pesticides.

Conflict of interest None

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