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Assessment of hematological parameters in workers exposed to organophosphorus pesticides, carbamates and pyrethroids in Cundinamarca 2016-2017

Evaluación de parámetros hematológicos en trabajadores expuestos a pesticidas organofosforados, carbamatos y piretroides, Cundinamarca 2016-2017

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ABSTRACT

Objective To establish hematotoxic alterations through clinical and paraclinical exploration in workers who are exposed to organophosphorus pesticides, carbamates and pyrethroids (OPCP) due to their work in production, packaging, distribution and fumigation processes in Cundinamarca-Colombia between 2016 and 2017.
Materials and Methods A cross-sectional descriptive epidemiological study was carried out on a sample of 92 workers from six companies, mostly aged between 18 and 30 years, of which 61 % were males and 39 % females, and 71 % were workers in the operational area and 29 % in the administrative area. Univariate, bivariate and multivariate analyses were performed.
Results Clinical exploration reported findings in 17 % of the sample group, of which only 2 % presented with erythrocyte cholinesterase outside the reference range. The values of hematological parameters such as peripheral blood smear (PBS) and complete blood count (CBC) were outside the range in 15 % and 47 % of the sample, respectively.
Discussion The results suggest that there are hematological alterations in this group that could possibly be associated with chronic exposure to OPCP.

Key Words: Pesticides, organophosphorus compounds, carbamates, lipid peroxidation, oxidative stress, blood cells, acetylcholinesterase *(source: MeSH, NLM)*.

RESUMEN

Objetivo Determinar las alteraciones hematotóxicas a través de una exploración clínica y paraclínica, en trabajadores que por su oficio se exponen a pesticidas organofosforados, carbamatos y piretroides (POCP), en procesos de producción, envase, distribución y fumigación, en el departamento de Cundinamarca Colombia.
Metodología Se realizó un estudio epidemiológico descriptivo de corte transversal. Se realizó un análisis univariado, bivariado y multivariado. La muestra se conforma por 92 trabajadores de seis empresas, la mayoría entre los 18 y 30 años, de los cuales el 61 % son hombres y el 39 % mujeres, 71 % se desempeñan en el área operativa y 29 % en el área administrativa.
Resultados Es de resaltar que se tienen hallazgos en la exploración clínica en el 17 % del grupo participante, solo el 2 % presenta la colinesterasa eritrocitaria por fuera del rango de referencia. Los parámetros hematológicos como el frotis de sangre periférica (FSP) presentan valores por fuera de los rangos en el 15 % y el cuadro hemático (CH) tiene valores por fuera de los rangos en el 47 % de las personas.
Discusión Los resultados sugieren que existen alteraciones hematológicas en este grupo y que posiblemente podrían estar asociadas con la exposición crónica a POCP.

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Palabras Clave: Toxicidad pesticidas, organofosforados, carbamatos, peroxidación de lípido, estrés oxidativo, células sanguíneas, acetilcolinesterasa *(fuente: DeCS, BIREME)*.

In the past few years, discoveries in Chemistry have yielded a large number of substances that are used in crops, including insecticides. Based on their origin, organochlorines and OPCP are classified in the organosynthetic pesticides group, which is synthesized in the laboratory and contains carbon, hydrogen and one or more elements such as chlorine, phosphorus, nitrogen, sulfur, among others (1).

The most common pesticides used in Colombia are part of the organosynthetic group, whose action is based on the chemical nature of the functional group, providing all the physicochemical and toxicological properties to the pesticide. Due to their high demand, greater toxicity, persistence and residuality, organosynthetic insecticides have been widely studied. In Colombia, organochlorines were banned, being Lindane for agricultural use and DDT the last ones commercialized (1).

Several studies have suggested that these compounds, when in contact with the organism, produce toxic alterations in the nervous system, and that one of the molecular mechanisms involved in the toxicity of organochlorines and POCP is lipid peroxidation. During this process, reactive oxygen species (ROS) can increase intracellular oxidative processes, causing alterations in the membranes of certain blood cells, especially red blood cells, since their membrane is rich in polyunsaturated fatty acids, iron of the heme group and oxygen, elements that are capable of producing oxidative changes in red blood cells (2).

Experimental studies have shown both increases and decreases in enzymatic antioxidant activity in rat erythrocytes and in in vitro assays with cell cultures. On the other hand, studies in humans have been contradictory, since they show an increase of erythrocyte antioxidant enzymes in fumigators with more than 5 years of exposure to pesticides, while others point to a decrease in these erythrocyte enzymes in acute organophosphate poisonings (3).

Regarding alterations in blood cells, some studies show that white blood cells, lymphocytes, monocytes and platelet counts are higher in workers who handle pesticides than in controls. Hemoglobin and hematocrit were lower in the farmer group compared to controls (4).

According to the study conducted by Varona, the laboratory test used on admission and for monitoring workers to determine exposure to pesticides is acetylcholinesterase. However, most companies use it arbitrarily to assess exposure to all types of pesticides. Furthermore, other non-specific diagnostic tests are used to assess the effect of pesticides on human health (5).

In Colombia, studies of the effects of OPCP on blood cells in an occupationally exposed population are not available. Therefore, carrying out studies to know the changes of the hematological parameters and to identify if they can be used as biomarkers of effect in this population are necessary.

The country can turn into a suitable scenario for epidemiological research on chronic adverse effects by these compounds, especially taking advantage of working populations (6).

MATERIALS AND METHODS

An epidemiological cross-sectional study was carried out based on data collected between the second semester of 2016 and the first semester of 2017.

Population and sample: The universe was made up of workers exposed, because of their jobs, to OPCP during production, packaging, distribution and fumigation processes. Six companies that carried out activities of preparation, packaging, storage, transportation of pesticides, and eradication of pests in Cundinamarca-Colombia, and manipulated OPCP as well, were included in the study. The sample consisted of 92 workers, mostly aged between 18 and 30 years, 61 % male and 39 % female, 71 % from the operational area and 29 % from the administrative area.

Instruments for gathering information: A toxicological history was elaborated with emphasis on hematological alterations, through a medical examination carried out directly by the researcher. Subsequently, blood samples were taken to measure erythrocyte cholinesterase activity, CBC and FSP. The observed variations were evaluated with respect to the reference values given by the laboratory.

Information Analysis: The results were entered in Excel® and analyzed with the epi-info® 7.2.1.0 and SPSS® programs. Univariate, bivariate and multivariate analyses were performed, for which statistical tests were used, including chi-square for qualitative variables, correlation coefficient for quantitative variables, and Student's t-test for qualitative vs. quantitative variables. The results of the paraclinical tests and the medical assessments were analyzed.

RESULTS

Table 1 shows that most workers were males who worked in the operational area in positions such as technical applicator (32 %) and production assistants (15 %). The population was mainly young, with secondary education,

exposed to pesticides from 1 to 10 years, and daily exposure between 1 to 5 hours. 82 % reported the use of personal protection equipment (PPE) since they had direct exposure to OPCP. Only 2 % of the workers reported a history of pesticide poisoning; one of them required hospitalization with no sequelae at the time of the interview.

Univariate Analysis

Table 1. Physical characteristics, personal habits and occupational variables of the study subjects

Variables	n (%)	Mean±SD
Female sex	36 (39)	
Male sex	57 (61)	
Age (years)		34.3 ± 10.8
BMI (weight/size^2)		24 ± 3.9
Systolic BP		111 ± 12
Diastolic BP		70 ± 9.2
Symptomatology	38 (41)	
Findings on PE	17 (15)	
Physical activity	35 (38)	
Smoker	37 (40)	
Alcohol users	9 (10)	
Illegal drug users	1 (1)	
Drug users	25 (27)	
Pesticide poisoning	2 (2)	
Contact with pesticide (hours/day)		4 ± 3.2
Length of exposure (months)		49.4 ± 51.3
Administrative performance area	27 (29)	
Operational performance area	65 (71)	
Use of EPP	82 (89)	

Source: Own elaboration based on the data obtained in the study

Physical examination (PE) was abnormal in 17 % of the sample, finding a person with a murmur, jaundice in two persons, mucocutaneous pallor without alterations of capillary refill in four, atrophy of lingual papillae in three, peeling nails in three, and adenomegalies in five.

Laboratory tests revealed abnormal findings of values outside the reference range in 2 % for cholinesterases, 47 % for CBC, and 15 % for FSP. Table 2 and Table 3 presents the analysis of each test.

Bivariate Analysis

The two men with erythrocytic cholinesterases outside the range were workers of different companies; they were fumigation operators, with direct exposure to OPCP. One presented cholinesterase below the reference range (1 1076 U/L) and the other above the rage (17 451 U/L).

The worker with levels below the range was 35 years old and had been directly exposed to OPCP for five years. He reported daily exposure of four hours, used PPE, and denied a history of pesticide poisoning, cigarette smoking, alcohol use and pathological history. In addition, he did not take prescription drugs and occasionally self-medicated dipyrone. FSP and CBC were normal.

The worker with results above the cholinesterase range was 56 years old and had been directly exposed to OPCP for eight years. He reported daily exposure of two hours, using PPE, smoking 70 cigarettes per week for 44 years,

Table 2. Cholinesterase results

Normal values	Staff of the administrative area with altered cholinesterase. n=0 n (%)			Staff of the operational area with altered cholinesterase. n=2 n (%)			Total %
11188 to 15698 U/L	Below the range	Above the range	Total	Below the range	Above the range	Total	
	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)	2 (2)

Source: Own elaboration based on the data obtained in the study.

Table 3. Complete blood count results

CBC profile	Normal values	Staff of the administrative area with altered cholinesterase n=13 n (%)			Staff of the operational area with altered cholinesterase n=46 n (%)			Total %
		Below the range	Above the range	Total	Below the range	Above the range	Total	
Hb	(M: 12,5-15,5) (H: 14,5-17,5) g/dL	1 (1.4)	2(2.8)	3(4.2)	2 (2.9)	2 (2.9)	4 (5.8)	10
Ht	(M: 35-46,5) (H: 42-52) %	0 (0)	3 (4.5)	3(4.5)	0 (0)	5 (7.5)	5 (7.5)	12
RBC	(M: 3,9-4,9) (H: 4,5-6) mill/uL	0 (0)	8 (12.2)	8 (12.2	0 (0)	7 (10.7)	7(10.7)	23
MCV	(82-98) fl	2 (3)	0 (0)	2 (3)	0 (0)	2 (3)	2 (3)	6
HCM	(27-33) pg	2 (2.7)	0 (0)	2(2.7)	0 (0)	1 (1.3)	1 (1.3)	4
CHCM	(32-36) g/dL	3 (4.8)	0 (0)	3(4.8)	7(11.2)	0 (0)	7(11.2)	16
RDW	(11,6-15,5) %	0 (0)	1 (1.4)	1(1.4)	1(1.35)	1 (1.35)	2 (2.7)	4
GB	(4.5-10) 10^3/mm	0 (0)	2 (3)	2 (3)	1 (1.5)	6 (8.5)	7 (10)	13
N	(45-74) %	0 (0)	0 (0)	0 (0)	4 (6)	0 (0)	4 (6)	6
L	(16-45) %	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.5)	2 (1.5)	3
M	(3-10) %	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1
E	(0-7) %	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	1
PLAT	(150-500) 10^3/mm	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1

Source: Own elaboration based on the data obtained in the study. Hemoglobin (Hb), Hematocrit (Ht), Red blood cells (RBC), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Red cell distribution width (RDW), White blood cells (WBC), Neutrophils (N), Lymphocytes (L), Monocytes (M), Eosinophils (E), Basophils (B), Platelets (PLAT).

weekly alcohol consumption (beer), a history of hypertension under treatment with Losartan, no self-medication and no history of pesticide poisoning. PE found BMI of 28, lingual papillary atrophy and mild neck enlargement. FSP reported mild leukocytosis and CBC revealed leukocytosis, polycythemia at the expense of increased hemoglobin concentration, hematocrit, red blood cell count (RBC), and red cell distribution width (RDW) count.

Student's t test did not show significant differences for the variables sex, work area vs cholinesterase.

The highest proportion of hematological alterations was found in the red cells, especially the RBC count above the reference ranges, followed by CHC below the reference values, and WBC above the given ranges.

When applying the chi-square, t-student and correlation coefficient statistical tests on the described variables and the results of the table, no statistical dependence nor significant differences or association were obtained.

The remaining statistical tests for the comparison of the variables described in Table 4 vs. the findings in the FSP did not show associations.

Table 4. Findings with a greater proportion of alterations in the blood picture

Variables	%
Administrative women	44
Over 50 years	56
Seniority between 1 and 10 years	48
Daily exposure from 6 to 9 hrs	65
No EPP	70
Physical activity	49
Cigarette consumption	49
Pathological history	55
Medication	60
Pesticide poisoning	100
Symptomatology	55

Source: Own elaboration based on the data obtained in the study

The FSP showed some type of abnormality in the count or morphology of the cell lines by 15 %. The alterations corresponded to mild leukopenia, leukocytosis, erythrocytosis, microcytic – normochromic RBC (+) and thrombocytopenia (Table 5). 85 % of the participants had a normal FSP.

The chi-square test for comparing the qualitative variables found that using PPE and FSP alterations are dependent parameters, and dependence is statistically significant, therefore, they are correlated: Chi-square experimental value (x^2 *exp*): 5.31; Critical chi-square value (x^2 *critical)*: 3.84, for which the null hypothesis is rejected, since the x^2 *exp* value is greater than the x^2 *critical* value; OR=4.8, which indicates that workers who do not wear PPE have a greater risk of presenting alterations in FSP.

Table 5. Peripheral blood smear results

Type of alteration	Staff of the administrative area with altered FSP. n=5 n (%)	Staff of the operational area with altered FSP. n=9 n (%)	Total %
Leukocytosis	2 (2)	3 (3)	5 (5)
Leukopenia	0 (0)	2 (2)	2 (2)
Poliglobulia	2 (2)	3 (3)	5 (5)
Microcytosis	1 (1)	0 (0)	1 (1)
Thrombocytopenia	0 (0)	1 (1)	1 (1)

Source: Own elaboration based on the data obtained in the study.

Multivariate analysis

A strong correlation in workers exposed 6-9 hours to pesticides and those who have been handling them for 1 to 10 years was observed regarding CBC findings: white blood cells WBC (-) and monocytes M (-) below the reference range, and leukopenia in the FSP.

Additionally, a strong correlation was found between female sex with polyglobulia in the FSP, and eosinophils E (+), RBC (+) and Hb (+) above the ranges in the CBC. A clear correlation was found between indirect exposure and the administrative area. These variables were also associated to MCV (-) below the reference range in the CBC and microcytic-normochromic RBC in the FSP.

Finally, an association was observed between exposure time greater than 10 years and CHC (+) above the reference range, RDW (-) below the reference range and leukopenia in the FSP.

DISCUSSION

In the population studied, erythrocyte cholinesterase activity was found outside the reference ranges in 2 % of workers. The study did not consider basal cholinesterases before exposure for comparison with periodic or post-exposure cholinesterases and to measure the degree of inhibition or the percentage of variation (7), taking into account interindividual and intraindividual variations, age and the presence of diseases related to erythrocyte cholinesterase. (8)

One of the two workers with alterations presented polyglobulia, which coincides with the literature consulted (8), where erythrocyte cholinesterase shows an increased activity in this type of pathology; leukocytosis in CBC and FSP, high blood pressure (HBP) and heavy smoking were evidenced as well. It could be inferred that the worker, being a chronic smoker, could be in a hypoxemic state, which requires a greater production of red cells as a compensatory mechanism. Taking into account that acetylcholinesterase is produced in the RBC, a polycythemic state would result in an increased synthesis of this enzyme.

In the CBC, the most frequent alterations were an increase in the RBC count by 23 % —which differs from studies such as Mohd (9)—, followed by a decrease in the

by 15 %, which is in line with the results of the studies of Parron and Fareed (9,10).

Contrary to Wafa (4), who reported that Hb and Ht concentrations significantly decreased in the population chronically exposed to pesticides, this study found an increase in Ht concentration by 12 % and in Hb by 6 %.

Moreover, this works differs from Hundekari (11), who found a significant decrease in the Hb value in the organophosphorus poisoning group, based on the assumption that the red line, due to multiple oxidative changes, is one of the most sensitive to changes by free radicals attack with subsequent lipid peroxidation.

In this study, leukocytosis was observed in 12 % of CBC alterations. This coincides with the studies conducted by Wafa (4) and Hundekari (11), who reported leukocytosis in the exposed population compared to controls, which could be considered as a defense mechanism of the immune system to OPCP exposure.

Wafa (4) reported significantly high lymphocytosis, monocytosis and platelet counts in the exposed population, whereas this study found lymphocytosis in only 3 % of the population and no individuals with monocytosis or high platelet count. Furthermore, Fareed (8) reported significant alterations in neutrophil, monocytes and platelet counts, while this study revealed that people with CBC alterations had changes in these cells only by 6 %, 1 % and 1 %, respectively.

The highest proportion of alterations in the CBC was found in administrative women, with RBC above the range (44 %). In this group, WBC above the range (13 %), MCV below the range (13 %) and MCHC below the range were also observed, which is related to hematotoxicity produced by the pesticides of interest and could be attributed to the lack of use of EPP by most administrative workers, considering that they share the same work area where chemical products are stored or processed.

The highest proportion of CBC alterations occurred in people over 50 years of age (56 %), in those who had been in contact with pesticides from 1 to 10 years (48 %) and those who had been exposed for 6 to 9 hours a day (65 %). The most common alterations in these groups were Ht (+), MCHC (-), RBC (+), and WBC (+), which could be explained by the presence of chronic diseases in age groups, the possible use of hematotoxic drugs, chronic exposure to OPCP, longer exposure in relation to the amount of worked days, and the meters above sea level of the housing site.

A greater proportion of alterations in the blood count was observed in workers who do not use PPE (70 %), and from higher to lower frequency: RBC (+), WBC (+), Hb (+), Ht (+) and MCHC (-). The changes observed in WBC and MCHC coincide with different studies that state that OPCP cause alterations in the blood cells, particularly when a person does not have adequate means of protection (3,4).

A higher proportion of values outside the reference ranges in the blood count was also observed in people who performed physical exercise (49 %), showing, from higher to lower frequency, RBC (+), Hb (+) and Ht. This could be explained by the greater metabolism in the red cells, since they oxygenate the tissues when they increase their metabolic demands. Likewise, greater CBC alterations were found in smokers (49 %), with a greater frequency of RBC (+), which can cause hypoxemia with compensatory production of blood cells, especially red cells. A higher proportion of alterations in the CBC was also found in people who had a pathological history (55 %) and in those who used formulated drugs (60 %), which is expected taking into account that some pathologies and medications can significantly alter blood parameters because CBC is a highly susceptible test.

The only two workers who reported a history of pesticide poisoning presented CBC alterations (100 %), with neutropenia being the only finding, which differs from the study conducted by Wafa (4), who reported an increase in the granulocytes count as a defense mechanism of the immune system when exposed to pesticides.

The FSP used in the clinic to assess anisocytosis (alterations in size) and poikilocytosis (alterations in shape) of the blood cells showed some type of count or morphology abnormality in 15 % of the studied population. The main alterations were mild leukopenia, leukocytosis, erythrocytosis, microcytic - normochromic red blood cells (+) and thrombocytopenia. The tests of the remaining 85 % were normal.

Regarding white cells, two people had mild leukopenia and five leukocytosis (8 % of the total population), all with normal morphology. In the erythroid cell line, abnormality was reported in 7 % of the total population, five with an increased number and normal morphology, and a person of the administrative area that presented microcytic -normochromic red blood cells (+). In relation to the platelet line, only one worker (1 %) of the operative area (applicator technician) had a decrease in the count with normal morphology. None of the international studies reported platelet alterations, therefore, the findings of this study were not subjected to comparison.

The highest proportion of alterations in the FSP occurred in administrative women, followed by operative women, which coincides with the CBC results. In the operational area, the highest proportion of alterations in the FSP was found in production assistants, followed by technical applicators. The highest proportion of alterations was found in workers older than 50 years, those who did

not use PPE, those who did not consume alcohol, those who had or have any disease, those who used formulated drugs, those with a history of pesticide poisoning, and those who presented symptoms. These results match the CBC and can be explained by the same causes mentioned above. The alteration of the hematological parameters in the studied population is evident, especially in the red and white cells, as observed in this study.

Some associated variables such as pathological history, medications, toxic habits, physical exercise and even age, sex and housing site, could generate alterations in the results since they are extremely variable before any change in the homeostasis of the human body. Once the possible confounding variables were analyzed, no statistically significant association was found with changes in the FSP and CBC. Thus, it can be inferred that OPCP can produce alterations in the hematological parameters studied.

This conclusion would be supported, as shown by this study, by the fact that the highest proportion of alterations in the hematological parameters was found in the workers of the administrative area, who usually do not use PPE and are exposed in an indirect way to the toxic substance during a significant percentage of the working day, and by the proximity of their working site with the areas of production and/or storage of chemicals. Additionally, a significant association was found between not using PPE and alterations in the FSP, which indicates that workers who do not use PPE have a higher risk of presenting alterations in the FSP.

The results of this study are consistent with those reported in the international literature, which shows evidence of a decrease in the red cell count and an increase in the white cell count, supporting the assertion that these pesticides, by means of lipid peroxidation, alter the red cell count and activate a defense mechanism of the immune system with an increase in the number of white cells. The alterations in erythrocyte cholinesterase did not have significant relevance in this study; however, the indicated procedure is to compare cholinesterase before exposure or periodic cholinesterases after exposure, given the mentioned variations.

Analytical studies with control populations are recommended for future research in order to compare exposed and non-exposed samples. Implementing environmental measurements at working sites would allow a better characterization of the exposure, as well as a high turnover within the different activities of the company. It would be ideal to have more information from the companies.

Additionally, performing longitudinal studies would be of interest, where pre-exposure paraclinicals are taken and can be compared with paraclinicals during or after exposure to obtain follow-up results and greater reliability in the behavior of the hematological parameters.

Due to the difficulties experienced when obtaining the samples, including the refusal of some companies to participate and the scarce information provided, it is evident that Colombia does not have any kind of regulation to obtain the necessary information for this type of research. Proposals could be made through control entities or associations to sensitize and raise awareness among legal representatives and employers about the importance of this type of research, since the health of the workers is expected to be the priority for the companies and not only operating activities, as in most cases.

The results of this research should serve as an initial approach to a problem that has not been studied in our country. Subsequent studies may lead to implement CBC and FSP for epidemiological surveillance programs directed to workers at chemical risk due to the exposure to hematotoxic substances, since their cost is low and they are accessible.

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