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Study of Serum Cholinesterase Levels Among The Farmers exposed to Pesticides in Kakinada District: A Cross-sectional Study

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Abstract

Introduction: A vast majority of the population in India (56.7%) is engaged in agriculture and is therefore exposed to pesticides. Unsafe and non-preventive work practices in handling and spraying of organophosphorous compounds has endangered the agriculture workers to its toxic effects. Enhanced risk of exposure among the farmers and agricultural labourers, might cause serious adverse health effects and negative socio-economic impact.

Objectives: To estimate serum Cholinesterase levels among the farmers exposed to pesticides along with age and sex matched healthy controls and see whether they are statistically significant or not.

Methods and Materials: Based on inclusion and exclusion criteria total number of 50 cases and 50 age and sex matched controls were selected for the present study. Their age group varied from 40 to 70 years. Serum cholinesterase is analysed on Beckman-Coulter AU480 automated analyzer, by Butyrylthiocholine kinetic method.

Results: Results show that the agricultural workers who had occupational chronic exposure to pesticides showed decreased cholinesterase levels. ($p < 0.0001$: extremely statistically significant).

Conclusion: The present study implies that serum Cholinesterase levels should be monitored on regular basis among the farmers, to predict the ill-effects of chronic pesticide exposure and to evaluate potential intervention measures to reduce the burden of disease.

Keywords: Pesticides, Organophosphorous compounds, Serum Choliestera

Introduction

Pesticides are chemicals that are used to control pests and improve agricultural productivity. Organophosphate and Carbamate compounds are a group of pesticides that are mainly used in agriculture [1]. Use of them has increased tremendously in developing countries like India especially after the green revolution [2]. However, unsafe and non-preventive work practices in handling and spraying of pesticides has endangered the agriculture workers to its toxic effects [3]. Besides the environmental concerns on excess use of pesticides [4], there are also concerns regarding the enhanced risk of exposure among the farmers and agricultural labourers, which might cause serious adverse health effects and negative socio-economic impact [5]. In most of the Asian countries, the World Health

Organization's (WHO) class I and II organophosphates and carbamates are the most frequently involved pesticides causing accidental, unintentional and occupational poisoning [6].

Routes of human pesticide exposure may be direct or indirect. Direct exposure include dermal absorption, inhalation, ingestion and indirect exposure is via food chains in pesticide treated crops. The adverse health effects of pesticide exposure vary from short-term (skin irritation, eye irritation, headache, dizziness and nausea) to chronic health impacts (asthma, diabetes and cancer) [7]. Chronic exposure to organophosphorous compounds are prone to develop neurotoxicity, congenital anomalies and cancers [8]. Pesticides have been proved to have hematotoxic effects and may trigger aplastic anemia, leucopenia, and thrombopenia to different cytopenias [9]. Similarly, chronic exposure is linked to many hematological malignancies like, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) [10]. Organophosphates have been associated with chronic neurological disease such as impaired memory, impaired fine motor skills control and Parkinson's disease [11].

Acetylcholinesterase is an enzyme that breaks down the acetylcholine (ACh) into choline and acetic acid [12]. Organophosphorous (OP) and Carbamate 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 [13]. Many developing countries implement bio-monitoring and surveillance programs intended to protect farmers from the adverse effect of pesticide exposure. Monitoring programs are undertaken to detect early physiological changes before resulting in reversible or irreversible diseases and illness. The globally accepted monitoring programs include the measurement of peripheral cholinesterase enzymes: the erythrocyte and serum cholinesterase/ pseudocholinesterase [14]. 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 enzyme [15]. 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 [16]. They are easy to measure, sensitive methods are available and the serum levels are also linked with adverse health effects in the exposed persons [17] and hence taken as parameter for present study.

A vast majority of the population in India (56.7%) is engaged in agriculture and is therefore exposed to pesticides. Currently India is the largest producer of Pesticides in Asia and ranks 12th in the world among pesticide usage [18]. Uttar Pradesh, Maharashtra, Andhra Pradesh, Punjab and Haryana are the states that accounted for 70 per cent of total pesticide consumption [19]. However, a literature search revealed that there is a dearth of studies in India related to pesticide exposure and knowledge and awareness level of farmers on risks and hazardous effects of pesticides use. A study of the health effects of acute pesticide toxicity among the cotton growers of India, by Mancini et al., are some of the positive steps to fill this research gap [19]. Similarly, there are paucity of studies on pesticide exposure among the farmers in this region of Andhra Pradesh. Hence, in an attempt to address the above lacunae, the present study is undertaken to determine Serum Cholinesterase levels among the farmers who are exposed to pesticides in Kakinada region of Andhra Pradesh.

Aims & Objectives:

The aim of this study is to know the variations in serum cholinesterase levels in farmers exposed to pesticides compared to that of healthy controls.

The objectives of the study are-

(a) To estimate serum Cholinesterase levels among the farmers exposed to pesticides

(b) To estimate serum Cholinesterase levels among the age and sex matched healthy controls

(c) To compare the above values with age and sex matched healthy controls and see whether they are statistically significant or not.

Materials & Methods:

(i) Study Design: This is a cross-sectional study planned in Rangaraya Medical College/Government General Hospital, Kakinada, AP.

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(ii) Study Area: The study was conducted among the farmers and healthy controls for whom the investigations are done in Central lab, Department of Biochemistry, Government General Hospital, Kakinada.

(iii) Study Period: The study is conducted for a period of 5 months from July to November 2023.

(iv) Study Subjects: A total of 100 individuals between the age group 40-70 yrs, both males & females are included in the present study. They are divided into 2 groups as follows:

Group 1: 50 individuals who were involved in active farming of duration more than 10 years.

Group 2: 50 individuals who were age and sex matched healthy controls.

(a) Inclusion criteria: Farmers who have given consent/ willing to participate are included in the present study.

(b) Exclusion criteria: (1) Farmers who have no chronic exposure to pesticides.

(2) Farmers who did not give consent/ not willing to participate in the present study

(3) Farmers with any co-morbid conditions like-

a) Hepatic parenchymal diseases
b) Chronic malnutrition
c) Chronic infections
d) Pregnancy
e) Chronic illness like renal and cardiovascular diseases
f) Women on OCP's

(v) Ethical approval & Informed consent: Ethical approval is obtained from the Institutional

Ethical Committee before the start of the study. Informed consent is obtained from the study subjects before collection of blood samples.

(vi) Estimation of biochemical markers: Serum Cholinesterase levels are estimated in serum obtained from the blood sample drawn from study subjects. Serum cholinesterase is analysed on Beckman-Coulter AU480 automated analyzer, by Butyrylthiocholine kinetic method. Grossly hemolysed or lipemic or icteric samples were not used for analysis in the present study and are discarded. The values so obtained are noted in an excel sheet.

(vii) Statistical analysis: Qualitative data is expressed as proportion and percentage while quantitative data is expressed as mean+SD. p value is calculated using student t-test p value <0.05 is considered as statistically significant and p value <0.0001 is considered as extremely statistically significant. Statistical analysis is done using Microsoft excel and Graph pad software.

Results:

The results of the present study are shown in Table 1, Table 2 and Table 3 as follows:

Table 1: Gender distribution of cases and control group

Category	Cases	Percentage	Controls	Percentage
Males	34	68	32	64
Females	16	32	18	36
Total	50	100	50	100

Table 2: Comparison of Age in cases and control group

Category	Range (Years)	Mean (Years)	S.D
Cases n = 50	43 – 68	50.26	± 6.32
Controls n = 50	42 – 69	53.80	± 8.70

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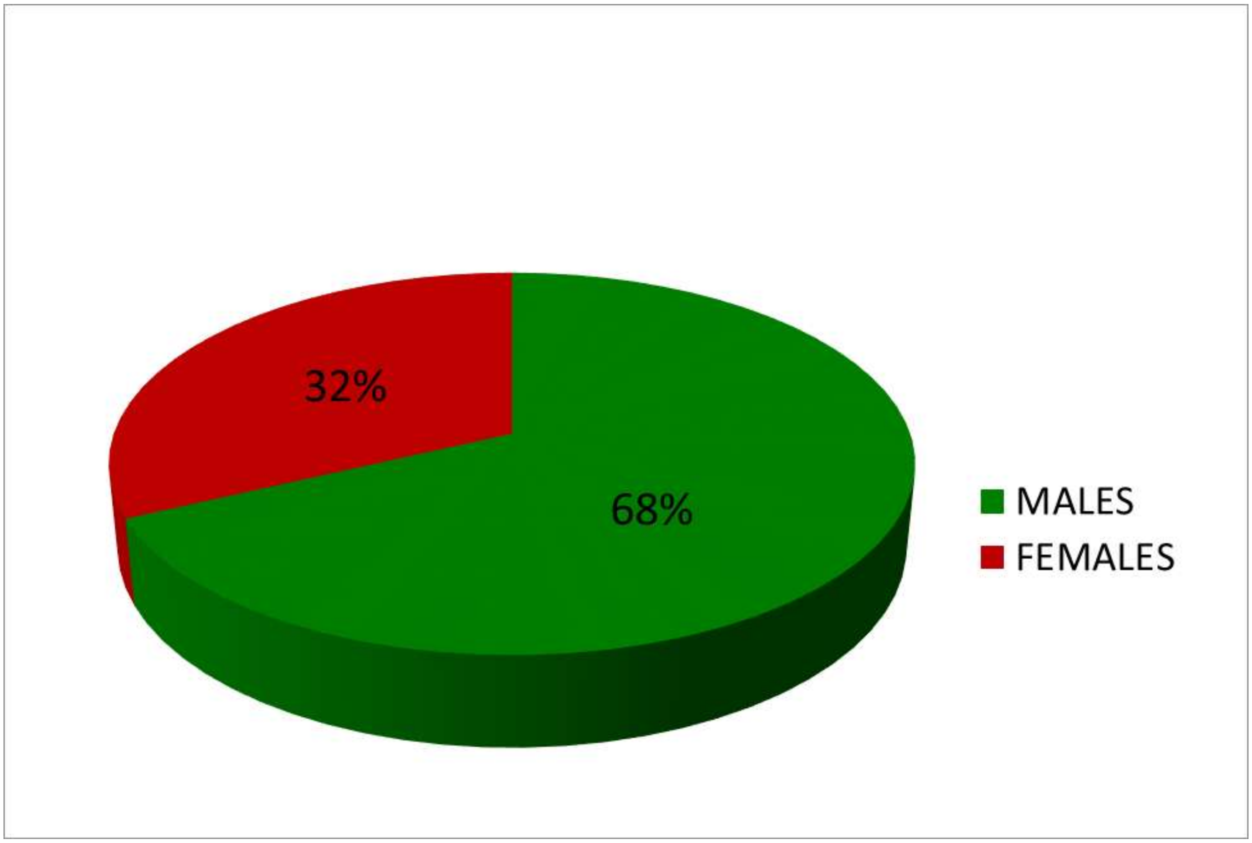
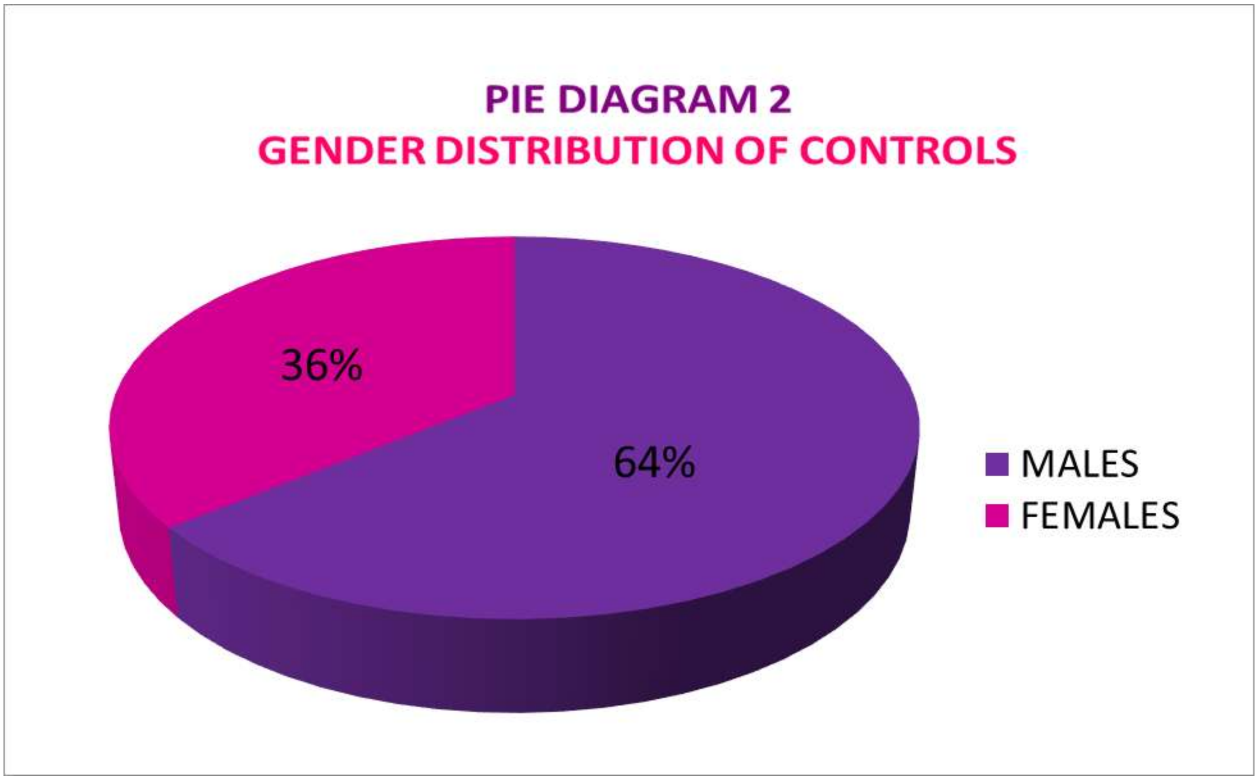
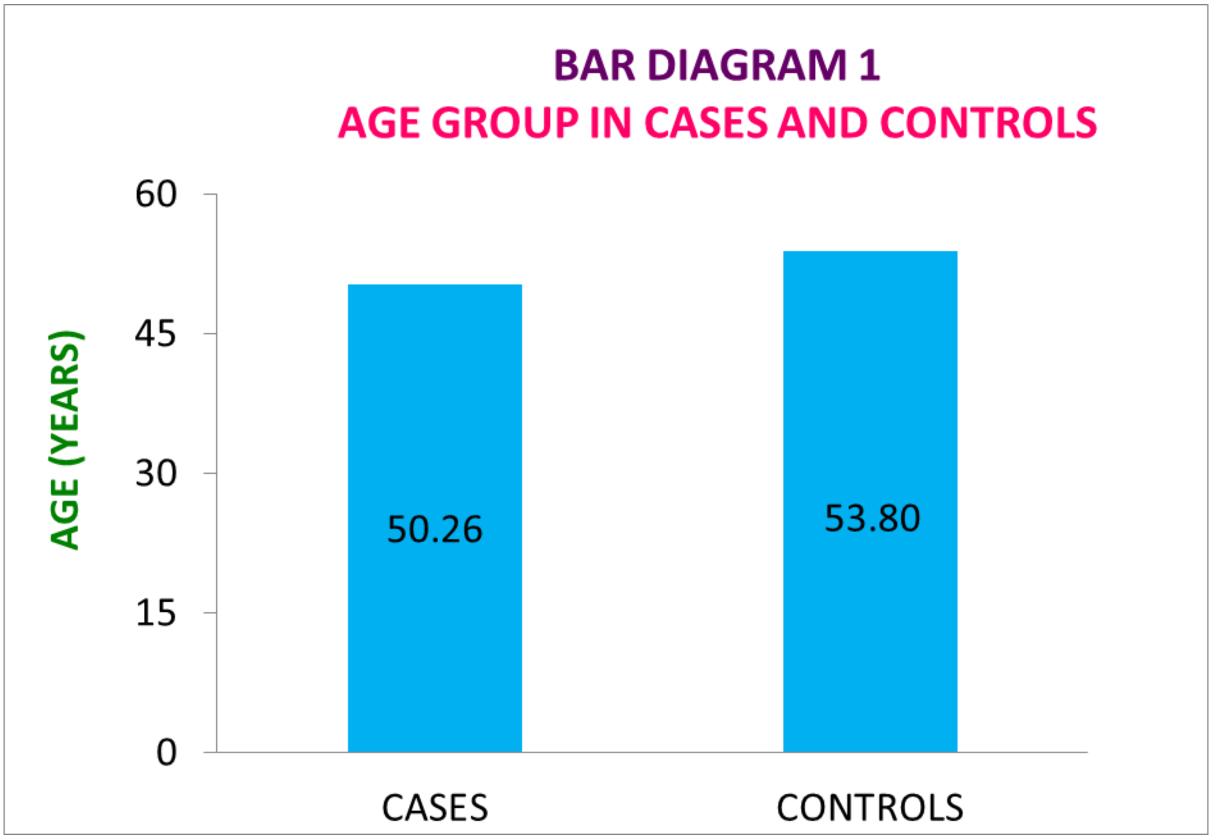
Table 3: Comparison of serum cholinesterase levels in cases and control group

Category	Range (IU/L)	Mean (IU/L)	S.D
Cases n = 50	2584 – 6018	4144.92	± 786.19
Controls n = 50	5012 – 9674	7078.88	± 1195.49







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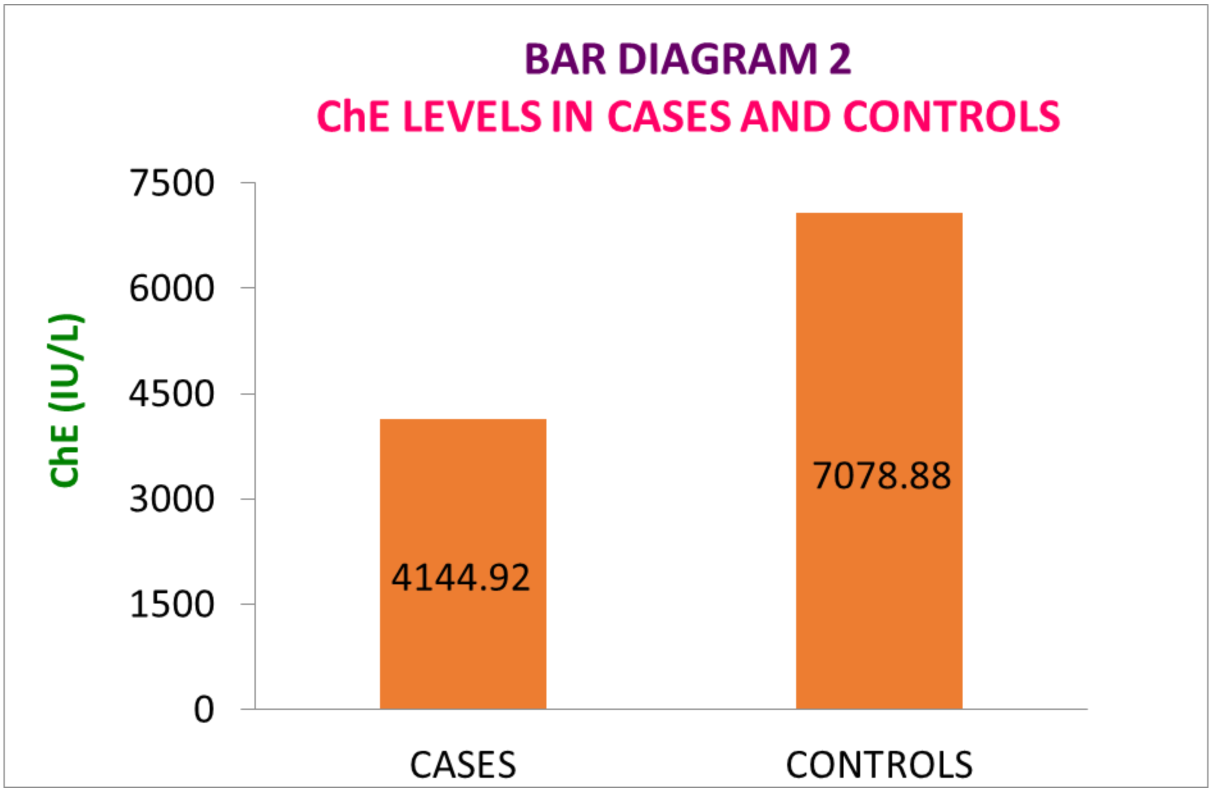

Discussion:

The use of pesticides in the developing countries is about 20% of the total world consumption since 1980 and it has been increasing annually [20]. It is estimated that around 800,000 people in developing countries may have died due to pesticides since the onset of the Green Revolution, and nearly 20,000 people die each year of pesticide exposure through various routes due to injudicious of hazardous chemical pesticides. Premature entry into sprayed fields or fumigated homes without proper protective equipment has caused acute organophosphate toxicity and death [21].

In contrast to organochlorine insecticides, organophosphate and carbamate insecticides degrade rapidly in the environment and do not accumulate or concentrate in the food chain. Thus, organophosphate and carbamate insecticides have less potential for physical health effects or environmental contamination than do organochlorine insecticides and pose less risk to consumers of food products. However, organophosphate and carbamate compounds have a greater potential for acute and chronic toxicity in humans than do chlorinated compounds. Organophosphate and carbamate compounds degrade in the environment at varying rates; half-lives range from days to months, although generally they are longer in dry climates and at low temperatures. As insects develop greater resistance, the trend is to use more potent, and consequently, more lipid-soluble and longer-lasting insecticides [22].

Present Study:

In our present study, it is shown that farmers exposed to pesticides had decreased levels of cholinesterase levels than the age and sex matched healthy controls. Our study is in agreement with other similar recent studies of H Sine et al (2019), Usha Kiran P et al (2019), Jaime Rosales R et al (2022) and Muhammad khan et al (2023) [23-26] as shown in the following table. However, a study conducted in Mexico reported that cholinesterase activity was not significantly reduced in the individuals exposed to pesticides [27].

1. Chronic exposure to pesticides was found in farmers who mix pesticides with marked inhibitions of acetylcholinesterase enzyme activity. It was also identified in the equation of multiple linear regressions with negative coefficients which means that every increase in

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the number of pesticides was mixed, then the level of acetylcholinesterase in the blood decreased, so there was inhibition of acetylcholinesterase. This was due to farmers who do not yet understand the additive and synergistic effects of chemical mixtures [28].

2. A study by Nerilo et al. (2014) carried out in the municipality of Maringa (Brazil), researchers observed a high inhibition in PC activity (> 30 %) in 4.6 % of the exposed workers (8/173) compared to the control group (p = 0.003).
3. Rosales (2015) determined the activity of the PC in a population of 109 individuals, 59 exposed farmers and 50 persons without exposure from the Virú district (Peru), where they found that the inhibition in the PC was significant (p < 0.001) between the exposed (4,733 ± 1,350.1 U/L) and the control groups (7,075 ± 1,674 U/L).
4. Cuaspud and Vargas (2010) analyzed the PC in 145 workers from the city of Tulcán (Ecuador), of which 95 farmers belonged to the exposed group, and 55 individuals were not exposed to pesticides (control group). The reference values ranged between 3,081 and 4,745 U/L, established from the average PC value of the control group (3,625.41 U/L), in a range of 3,081 to 4,745 U/L. These authors observed that of the total percentage of the exposed farmers, 44.21 % (n = 42) showed depressed PC activity values. When comparing the exposed group with the control group, they presented a statistically significant difference (p < 0.05) showing a value of 3,154.99 U/L in farmers, and 3,625.41 U/L in control group.
5. Lutovac et al. (2017) studied 175 workers in the chemical industry and agricultural production in the Rasina district (Serbia), including 78 workers of the pesticide production process, 50 agricultural workers, and 47 persons who were not exposed to pesticides; the results of the study showed that of the 128 workers exposed to pesticides, 72 % of the individuals, showed decrease in the cholinesterase activity.
6. However, contrary to the above studies, Butinof et al. (2017) reported no inhibition in the activity of the PC in any of the groups; the values for the exposed group were between 3,349.58 and 8,886.56 U/L, and for the control group, the values ranged between 3,292.10 and 7,289.48 U/L (reference value: 3,200 to 9,000 U/L) (p = 0.11). Similarly, Ortega et al. (2016) did not find statistically significant differences in PC activity between the group of exposed and unexposed farmers (p = 0.339).

Decreased serum cholinesterase levels - Mechanisms:

The decrease in serum cholinesterase levels in our present study and the toxic effects are due to a combination of various mechanisms. Insecticides are strongly lipophilic in nature and get incorporated into the bio membrane [29]. There are many studies in this aspect indicating role of insecticide compounds in inducing perturbations of membrane permeability and enzyme dynamics (Antunes-Madeira et al) [30]. Membrane mechanisms are based on the membrane physical state and organization (Sikkema et al). Hence the effects of insecticides are due to physical changes at the level of lipid-lipid and lipid-protein interaction [31].

Partition studies by Antunes-Madeira and Madeira, state that membrane undergoes modulation for the incorporation of insecticide. Lipids undergo rapid breakdown, re-synthesis and inter conversion [32]. Therefore, it is essential to study various lipid fractions in different tissues to provide a clear picture of lipid metabolism in response to pesticides which we have not done in our study. In a study done by Ghosh and Chatterjee, where B.dissimilis was exposed to pesticides, they found that there is decrease in tissue lipid and proteins under pesticide stress. It could be due to several mechanisms viz., formation of lipoproteins which are utilized for repair of damaged cell and tissue organelles, direct utilization by cells for energy requirements, increased lipolysis, and damage to cellular organization [33]. The mechanisms underlying chronic effects of pesticide exposure are largely unknown but are likely to be mediated by epigenetic changes such as DNA methylation and histone modifications [34].

The water solubility of some organophosphate and carbamate pesticides allows them to be absorbed by plants and act as systemic poisons in both mammals. Because these compounds are distributed rapidly throughout the body, they typically are associated with rapid onset of symptoms, rarely longer than a few hours after a toxic exposure. However, the more lipid-soluble organophosphates, such as chlorfenthion

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and fenthion, can undergo initial lipid storage with subsequent redistribution and may not produce medical crisis for several days. In the body, as well as in the environment, some organophosphates can be converted from the -thion form to the more toxic -oxon form; rates of conversion vary widely but are more rapid in vivo than in the environment. In the body, conversion is brought about chiefly by hepatic microsomal esterases. Ultimately, both the -thion and -oxon forms are usually metabolized to alkyl phosphates and other products that are of relatively low toxicity and are excreted rapidly. Carbamates are also metabolized in the liver, and the products are excreted in urine without evidence of significant [35, 36].

Some studies have corroborated that acetylcholinesterase enzyme inhibition is significantly associated with the increase in reactive oxygen substances, not only in workers who are exposed to OP pesticides, but also in those exposed to bipyridyl herbicides such as paraquat, which proves oxidative stress induction through an increase in lipid peroxidation and a decrease in antioxidant capacity [37]. As previously stated, ROSs increase oxidative processes within the cell and produce lipid peroxidation in cell membranes [38]. A biological effect has been suggested as a possible action mechanism of lipid peroxidation caused by pesticides on blood cells by means of an electrophilic attack on certain cellular components, process during which ROSs are generated [39]. A study conducted by Praksam et al [40] indicates that greater erythrocyte fragility and alterations in erythrocyte membrane fluidity, secondary to lipid peroxidation and generated by the oxidative stress caused by pesticides, have been observed in workers who apply them.

Limitations, Strengths & Future:

The main limitation of our present study is the small sample size and short study duration. Secondly, the study design did not control a number of confounding factors such as gender, previous exposure to OP's etc. Thirdly, no follow-up was done on health issues after collecting the blood samples. Nevertheless, an attempt was made to address the lacunae in this area of research. The blood samples are easy to collect, on which analysis can be done with minimal effort and minimal turn around time (TAT), to assess the toxicity, instead of tissue studies which are time consuming. However, specific observational studies on a larger sample size are to be carried out in future, which will help to formulate various interventional studies and surveillance programs. Such initiatives will protect the farmers from adverse effects of pesticide exposure.

Conclusion:

The present study revealed that agricultural workers who had occupational chronic exposure to pesticides showed decreased cholinesterase levels. The decreased levels are may be due to anti-acetylcholinesterase activity of organophosphorous and carbamate group of pesticides, which acts by phosphorylating the serine hydroxyl group present at the active site of acetylcholinesterase enzyme. Thus the present study implies that serum Cholinesterase levels should be monitored on regular basis among the farmers, to predict the ill-effects of chronic pesticide exposure and to evaluate potential intervention measures to reduce the burden of disease. The study can also be utilized as a means to promote health education among the farmers regarding hazardous health effects of using pesticides injudiciously and the need to practice of using basic personal protective equipment while handling pesticides.

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