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Evaluation of Chronic Haematological and Neurological Effects of Organophosphates Pesticides Exposure in Children of Rural Population

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Abstract: This is an award-winning study of its kind first time conducted in the rural areas of Indore Madhya Pradesh with the aim of evaluating the subclinical morbidity and mortality pattern of the chronic hematological and neurological effect of organophosphate pesticide exposure in children of farmers. Poison is any substance which if introduced into the living body could cause ill health or death. Among children, the commonest culprits include kerosene, pesticides, household chemicals, drugs. In rural areas of developing countries, children of agricultural workers have high probabilities for exposure to OP pesticides. This puts them at an increased risk of damage. A community-based cross-sectional study was carried out in 64 children aged 7-14 years in adjoining villages of khudel, Indore, Madhya Pradesh. Various neurological symptoms like muscarinic (diarrhea, urinary incontinence, lacrimation, excessive salivation), nicotinic (tremors, muscle weakness, tachycardia) and general symptoms (a headache, insomnia, numbness in legs, fatigue, anorexia, nausea, vomiting, dizziness, lethargy) were assessed by doing a clinical examination. Exposure index (EI) was calculated by multiplying the number of hours exposed to OP pesticides and the number of years of exposure. Various CBC parameters, metabolic panel (liver function test, kidney function test, FPG, vitamin B 12, electrolyte level) were calculated. The statistical evaluation was done using SPSS version 24.0 analysis of variance (ANOVA). The predominant clinical symptoms found in children in the study group were watering eyes (21.87%) burning sensation in the eyes (18.75%), nausea & vomiting (12.50%) a headache (6.25%). The nicotinic clinical manifestations were sweating (37.50%), tachycardia (25%), mydriasis (18.75%) with significant p-value for sweating (0.03) & tachycardia (0.02). The muscarinic clinical manifestations reported were lacrimation (31.25%), diarrhea (25%), and urinary incontinence (15.62%), and salivation (12.50%), significant p-value for diarrhoea (0.03). CBC analysis showed 58% of participants had at least one haematological abnormal indicator. Blood chemistry tests indicated an abnormal renal function in 4% of subjects, and aberrant hepatic function (9%), deranged electrolyte levels (11.2%), abnormal vitamin B-12 levels (8%), and abnormal fasting plasma glucose levels (13%) in subjects. Our study findings suggest that the high prevalence of neurological and haematological symptoms reported in exposed children could be attributed to chronic effects of OP pesticides on the CNS and Hematopoietic system.

Keywords: Haematological, Neurological, Organophosphates, Children.

INTRODUCTION

Organophosphate (OP) compounds although being primarily neurotoxic are used as pesticides and industrial chemicals on a large commercial basis. They may involve both central and peripheral nervous systems causing well-defined muscarinic, nicotinic and cholinergic neuro-symptoms [1]. The use of Pesticides in crop production worldwide increased nearly twentyfold from 1960 to 2000 [2] and further increased from 1.0 billion tons in 2002 to 1.7 billion tons in 2007 [3]. Despite the well-documented deleterious effects of pesticides on biological pest control function, the environment, and food safety [4–6], the health effects of these agents have also attracted substantial attention [7] Previous studies showed that pesticide exposure often induces acute and chronic neurological toxicity [8–13] and dysfunctional lipid, protein, and carbohydrate metabolism [14]. However, in most of the surveys subjective or qualitative measurements, such as symptoms, psychological scales, or clinical signs, have been used to evaluate the health effects of pesticide use on health [15–17]. Reviewing the literature it becomes evident that there are no recent studies conducted in the state of Madhya Pradesh where in the population is more than 80millions. The effects of pesticides on human beings have been replied by Khan and Ali, who

reported the adverse effect of organophosphate pesticides particularly on factory workers. No other work is available in literature hence the present study has been undertaken to investigate the chronic haematological, biochemical and neurological effect of organophosphate pesticide exposure to OP pesticides in children of farmers. Exposure to OP pesticides can occur through multiple pathways, including food contamination, environmental and household pollution, proximity to agricultural fields, and agricultural work. Children may be exposed to pesticides through farm work or as a result of school and/or household exposures [18-25]. The health effects of OP pesticides have been reported in numerous international studies. The studies have identified acute and chronic consequences of exposure to OP pesticides among farm workers and their children. It has also been observed that exposure to OP pesticides also constitutes an occupational hazard for people working on the farm and it may affect their children through the take-home pathway. If the pesticides are sprayed during the dry season, it may affect adversely the children of the farmers due to prolonged increased exposure to organophosphate[26]. In rural India, it has been evident that children of agricultural families have a great possibility of OP pesticide exposure. This exposure tends to increase during the activities of pesticide mixing, application, and intensive hand labour performed by the parents in treated fields. Chemicals may be brought into the home on work boots, tools, work clothing, or on the skin by the parents of children themselves or other family members while spraying pesticides. Moreover, exposure of children to pesticides may be greatly increased by household proximity to farms treated with pesticides which may enter into houses or other neighbourhood playing areas of children. In other cases, children may use fields as play areas, with or without the knowledge of their parents [27]. Prolonged exposure to pesticides being toxic to the brain may involve both central and peripheral nervous systems causing well-defined muscarinic, nicotinic and cholinergic neuro symptoms [28]. There have been only a few scientific studies which have estimated the extent of children's exposure to OP pesticide [29]. Since pesticide exposure in children has caused a rampant in rural areas of developing countries, the present study was carried out to assess the neurological risk of exposure to OP pesticides in children of agricultural workers in rural India.

METHOD

Study Design

A community-based cross-sectional study was carried out in 64 children from the adjoining villages of Index medical college Indore. Study (OP exposed) and control group both comprised of 32 rural children in each group, age 7-14 years belonging to similar socio-economic strata.

Inclusion Criteria

Children exposed to OP (study group) directly or indirectly were included. Children never involved in pesticide handling (neither outdoor nor indoor) and having no family history of pesticide exposure were included in the control group.

Exclusion Criteria

Parents who were not willing to allow their children to participate in this study, and children who were suffering from any disease which mimics the effects of OP poisoning like Gastroenteritis, asthma, influenza, pneumonia, hypoglycemia and those who were under medication were excluded because of negative influence on this study.

METHODOLOGY

- A detailed history regarding demographic variables, socioeconomic status, personal history and presenting complaints if any were recorded in the pre-structure survey proforma. In addition, complete clinical examination including general and systemic examination was done.
- The range of exposure was calculated as the number of hours exposed to organophosphate (OP) pesticides.Children have categorized accordingly as a range of exposure for < 1hr, 1- 4hrs and >4 hours.

Clinical examinations

The clinical examinations included general and neurological examinations. The former comprised height, weight, and blood pressure measurements.

Blood tests

All blood samples were obtained after participants had fasted for 12 hours. Samples were centrifuged immediately and transported in a refrigerated state to the same laboratory within 8 hours. The tests included a complete blood count (CBC), blood chemistry panel (e.g., liver function, cholinesterase, renal function, electrolytes, vitamin B12, folic acid, fasting plasma glucose) and measurement of C-reactive protein. All investigations were performed in the pathology and clinical biochemistry laboratory of INDEX Hospital, Indore. The sample for complete blood count and biomarkers analyses were collected, coded and processed on an SYSMEX X-800i auto analyzer for haematological parameters and biochemistry test by using semiautomatic biochemistry analyzer CHEM 7.

The obtained data were tabulated using MS Excel to create a master chart. The power of the study was kept at 99% and level of significance (α) at 5%. “Analysis of Variance (ANOVA)” was done to calculate the p-value to compare the difference of the mean of the study groups together. Post Hoc Turkey’s test” was also applied for comparison of the difference of mean in two study groups. The p-value was

calculated for each parameter and p-value <0.05 was considered to be significant. 95% CI was also calculated.

RESULTS

In the exposed group 34.37% children were girls and 65.625 were boys. Maximum numbers of children were in the age group of 11 to12 years. Maximum children had the exposure index of more than 4 hrs (Table 1, 2 &3). The prevalence of OP pesticide-related symptoms observed in exposed rural children was watering eyes (21.87%) burning sensation in the eyes (18.75%), nausea & vomiting (12.50%) a headache (6.25%) (Table 4 & Figure1). The nicotinic (Table 5) clinical manifestations were sweating (37.50%), tachycardia (25%), mydriasis (18.75%), significant p-value for sweating (0.03) & tachycardia (0.02). The muscarinic (Table 6 & Figure 2) clinical manifestations reported were lacrimation (31.25%), diarrhoea (25%), and urinary incontinence (15.62%), and salivation (12.50%), significant p-value for diarrhoea (0.03). CBC analysis revealed 58% of participants had at least one haematological abnormal indicator. Blood chemistry tests indicated an abnormal renal function in 4% of subjects, and aberrant hepatic function (9%), deranged electrolyte levels (11.2%), abnormal vitamin B-12 levels (8%), and abnormal fasting plasma glucose levels (13%) in subjects (Table 7).

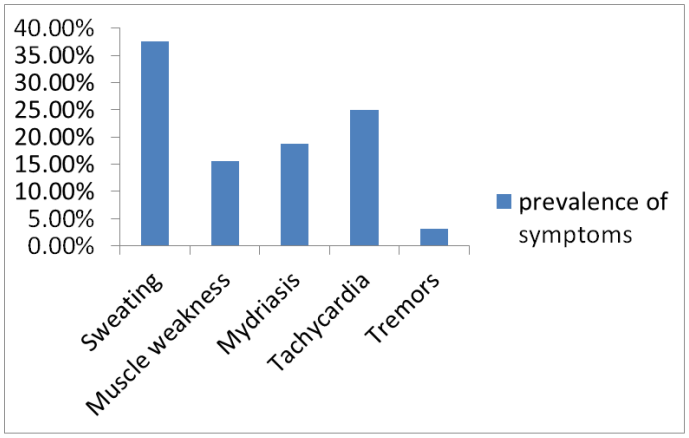

Fig-1: Prevalence of symptoms

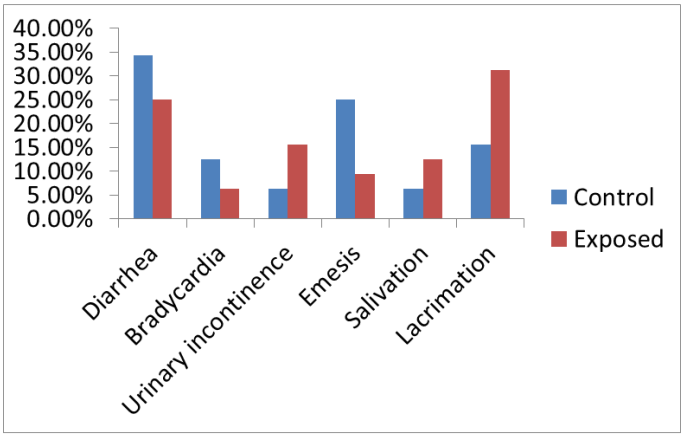

Fig-2: Comparison of muscarinic effects

Table-1: Sex-wise distribution

Group	Males (%)	Females (%)
Control	18 (56.25)	14 (43.75)
Exposed	21 (65.62)	11 (34.37)

Table-2: Age-wise distribution

Age distribution (years)	Control group (%)	Exposed group (%)
07 – 08	08 (25.0)	05 (15.62)
09 – 10	04 (12.50)	06 (18.75)
11 – 12	09 (28.12)	14 (43.75)
13 – 14	11 (34.37)	07 (21.87)

Table-3: Exposure index

Range of exposure	Exposed group	Control group (NA)
< 1 hrs	02	-
1 to 4 hrs	14	-
> 4 hrs	16	-

Table-4: Prevalance of pesticide-related symptoms

Symptoms	Control group (%) n=32	Exposed group (%) n=32
Headache	04 (12.50)	02 (6.25)
Burning sensation in eyes	03 (9.37)	06 (18.75)
Fever	10 (31.25)	04 (12.50)
Blurred vision	02 (6.25)	05 (15.62)
Weakness	02 (6.25)	01 (3.12)
Dizziness	04 (12.50)	03 (9.37)
Nausea and vomiting	06 (18.75)	04 (12.50)
Watering eyes	01 (3.12)	07 (21.87)

The prevalence of OP pesticide-related symptoms observed in exposed rural children was watering eyes (21.87%) burning sensation in the eyes (18.75%) blurred vision (15.62%),nausea & vomiting (12.50%).

Table-5: Clinical nicotinic manifestations

Symptoms	Exposed group (%)	p-value
Sweating	12 (37.50)	0.03
Muscle weakness	05 (15.62)	0.07
Mydriasis	06 (18.75)	0.08
Tachycardia	08 (25.00)	0.02
Hypertension	00 (00.00)	-
Tremors	01 (3.12)	0.23

None of the symptoms were present in the control group.

The nicotinic clinical manifestations were sweating (37.50%), tachycardia (25%), and mydriasis (18.75%) (Table 5).

The muscarinic clinical manifestations reported were lacrimation (31.25%), diarrhea (25%), urinary incontinence (15.62%), salivation (12.50%) (Table 6).

Table-6: Clinical muscarinic manifestations

Symptoms	Control group (%)	Exposed group (%)	p value
Diarrhoea	11 (34.37)	08 (25.0)	0.03
Bradycardia	04 (12.50)	02 (6.25)	0.40
Urinary incontinence	02 (6.25)	05 (15.62)	0.07
Emesis	08 (25.0)	03 (9.37)	0.23
Salivation	02 (6.25)	04 (12.50)	0.40
Lacrimation	05 (15.62)	10 (31.25)	0.08

Table-7: Percentage of Abnormalities in haematological parameters in the exposed group

Indicators	Percentage of Abnormalities
Blood Examinations	
Complete Blood Count	58%
Blood Chemistry test	
Hepatic Function	9%
Fasting Blood Glucose	13%
Renal Function	4%
Vitamin B 12	8%
Electrolytes	11.2%
C-reactive Protein	7.8%

DISCUSSION

This study was the first to comprehensively examine the human health for the effects of frequent pesticide exposure in Madhya Pradesh. In the hematological system, our study is consistent with some recent findings—alterations in CBC parameters are related to pesticides exposure [30]. Yet, it provides a better understanding of pesticide health effects in long- and short-term alterations. Specifically, only white blood cell count remains significantly increased over time. This might suggest that pesticides affect the hematopoietic function of bone marrow. The metabolic panel showed that pesticide exposure led to an acute hepatic dysfunction and FPG reduction, which was opposite to previous reports of pesticide associated hyperglycemia. Renal function was also affected as also shown in another previous study [31]. Due to the fact that children organ system are still under developing and growing, process the mechanism of chronic organophosphate toxicity has similarities and differences to that experienced by adults. Understanding the similarities and differences thus clarifies as to how chronic OP exposure may result in a wider range of illness or developmental deficits in children as compared to adults. Chronic exposure to organophosphates during development causes toxicity via distinct pathways. First, chronic over-stimulation at cholinergic nerve terminals results in neuronal damage in a mechanism similar to that seen in acute OP toxicity.

Chronic OP toxicity is characterized by

Subtle, often sub-clinical symptoms (compared to acute toxicity).

The variable time lag between exposure and illness (often not immediate) Because of these characteristics, connecting illness to chronic pesticide exposure appears to be difficult. Organophosphates are known to act on the nervous system, thus the research to date has largely focused on determining if chronic OP exposures cause neurodevelopmental effects. Both toxicological evidence (mostly from rodent models) and evidence from observational epidemiological studies support the idea that chronic organophosphate exposure can produce neurodevelopment deficits. Our findings revealed that general symptoms (Pallor, headache, anorexia, fatigue, dizziness, numbness in legs, insomnia, lethargy, nausea and vomiting) and among all the neurologic symptoms, muscarinic (diarrhea, lacrimation, salivation and urinary incontinence) and nicotinic (tremors and muscle weakness) were the most important clinical manifestations attributed to OP pesticide exposure. Moreover, the cognition and psychological function were more impaired in children exposed to OP pesticides than the non-exposed children [11]. Similar clinical findings have been reported a by other researchers. Farhat et al who studied the association between pesticide exposure and neurologic endpoints concluded that environmental and occupational exposure to OP pesticides leads to neurodegenerative functions in agricultural workers. Our study findings also conform to the findings of studies done by other investigators, which reported an increased prevalence of cholinergic symptoms like insomnia, anorexia, headache and numbness in legs in both male and female children as a result of chronic exposure to organophosphate pesticides. Rastogi SK *et al*. reported the maximum prevalence of muscarinic symptoms like salivation (18.22%), whereas lacrimation was noted in 17.33% cases, followed by diarrhea in 9.33% cases. The nicotinic clinical manifestations of acute OP poisoning revealed excessive sweating in 13.78% cases and tremors in 9.3% cases followed by mydriasis in 8.4% exposed children. Chronic exposure to most of the OP pesticides mainly affects the peripheral and central nervous systems which might cause important clinical neurologic manifestations, such as a headache, tremors, dizziness, and numbness [16]. Another important cause for pesticide-related neurologic symptoms, both muscarinic and nicotinic observed in the present study could be because of the inhibition of red blood cells, acetyl cholinesterase, as well as plasma butyl cholinesterase recorded in the study group. A similar mechanism has been reported in earlier previous studies [17, 18]. The long-term exposure to OP pesticides causing neurologic symptoms also leads to delayed toxicity since the breakdown of these chemicals in the body is slow resulting in the storage of pesticides in the body fat.

CONCLUSION

Low-level exposure induces a state of sensitization that therefore reduces the possibility of severe intoxication but do not avoid the possibility of mild chronic intoxication, we, therefore, suggest to identify sub clinical toxicity at an early stage and thereby to prevent the clinical manifestations of pesticides related disease at a later date. Also, there is a need to improve technique for early and accurate diagnosis and treatment. Further, it clarifies the need to establish a poison information center in this region for better management and prevention of such morbidity and mortality. Despite our incomplete understanding, the suggestive harm that chronic OP exposure poses to child development merits recommendations to parents to reduce pre- and postnatal exposure to pesticides, particularly OP's. It is concluded that there is a need for creating more awareness among the farm sprayers and authorities in implementing and ensuring the use of protective measures while handling pesticides. Farmers need to be encouraged to reduce, if not eliminate the use of pesticides and should be educated about bio-pesticides and their benefits, with the introduction of incentives to the farmers to help them shift from synthetic pesticides to bio pesticides and organic farming as new revolution can be as introduced.

Medico-legal Aspects

The symptoms of OPC poisoning can mimic other diseases. The clinicians must keep in mind that misdiagnosis is a potential medico-legal pitfall. Hospitalizing all symptomatic patients for at least 4-6 days following resolution of symptoms is recommended, because of the risk of development of respiratory depression or intermediate syndrome after resolution. Accidental poisoning occurs in manufactures, packers, sprayers and in children.

Limitation & Future scope of the Study

In the present study, the dose of exposure of OP was not documented. Information about exposure and symptoms among study and control group were collected by the same investigator hence some biases might have introduced in this study. Also, we could not measure the blood levels of OP due to time constraints. Nevertheless, the positive results obtained from the present study with more comprehensive exposure assessment, together with strong positive support from other studies, reinforces the hypothesis of an association between OP pesticide exposure and neurological abnormalities.

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