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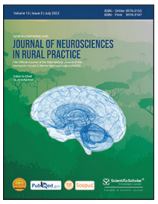

Brief Report

Associations between pesticide exposure with biomarkers of stroke risk factors in farmers

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ABSTRACT

The extensive use of pesticides may cause acute and chronic intoxication. Therefore, this study aimed to reveal the associations between pesticide exposure and serum markers for stroke risk factors in farmers. A cross-sectional study was conducted with farmers, who used chemical pesticides in Seloprojo Village, Ngablak District, Magelang Regency, Central Java Province, Indonesia. A questionnaire containing demographics, pesticide use, and aspects related to work was employed. Measurements of serum cholesterol, uric acid, glucose, cholinesterase, and fibrinogen levels were also conducted. Of the 106 subjects, 31 (29.2%) used organophosphates as chemical pesticides. There was a significant difference between organophosphate and non-organophosphate groups in plasma fibrinogen levels. The organophosphate group had higher levels of fibrinogen (292.29 ± 67.56 mg/dL) than the non-organophosphate group (255.24 ± 38.90 mg/dL). Of the studied risk factors for stroke, there is a significant association between organophosphate exposure and increased plasma fibrinogen levels.

Keywords: Pesticide exposure, Organophosphate, Fibrinogen, Stroke risk factors

INTRODUCTION

Farmers commonly use pesticides for pest control in order to keep their crops undisturbed by the pest as well as to improve the quality of the crops. The extensive use of pesticides may cause intoxication, both acutely and chronically.[1] Most studies focus on the acute impact of pesticide intoxication. Not only direct pesticide intoxication but also secondary inflammation reaction resulting from pesticide intoxication may cause atherosclerosis that can lead to cardiovascular events such as cardiac arrhythmia and coronary artery accidents.[2]

Chronic pesticide exposure is often linked to neuropsychiatric problems such as cognitive decline, attention deficit, and organophosphate-induced polyneuropathy.[3,4] Pesticide exposure is also associated with the increased probability and mortality of cardiovascular diseases such as hypertension and acute myocardial infarction.[2] It was also reported that there was an increased level of serum fibrinogen in farmers, who were exposed to pesticides, and its incidence was associated with the minimal use of personal protective equipment and the longer duration of pesticide exposure.[5] Increased level of fibrinogen is associated with atherosclerosis and coronary artery disease, peripheral artery disease, carotid stenosis, increased age, smoking, increased blood pressure, increased serum cholesterol level, and stroke.[6] Our study aimed to study the association between pesticide exposure and serum markers that are reported to be stroke risk factors such as serum fibrinogen, serum cholesterol, and blood glucose levels.

MATERIALS AND METHODS

A cross-sectional study was performed in 2018 in Seloprojo Village, Ngablak District, Magelang Regency, Central Java Province, Indonesia. The inclusion criteria for this study are farmers in the village, who were exposed to pesticides and consented for blood sampling. Farmers, who had a prior history of stroke, were excluded from the study. All subjects were informed about the course of the study and consented to complete the procedure. This study was approved by the Ethical Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, Ref: KE/FK/0424/EC/2018.

All farmers, who agreed to participate in the study, filled out a questionnaire consisting of age, years of education,

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and their working aspects such as working duration, personal protective equipment, type of pesticide used, their knowledge, attitude, and practice regarding pesticides. Physical examinations to assess body mass index and blood pressure were also performed. Personal protective equipment was assessed according to the World Health Organization's standard and scored according to the use of the equipment used by each farmer. The personal protective equipment score ranged from 0 (no personal protective equipment is used) to 100 (complete personal protective equipment is used). To determine the organophosphate exposure, each farmer was interviewed for the use of organophosphate including the amount and duration of its usage.

After completing the questionnaire and interview assignments, each farmer underwent blood sampling for the measurement of serum total cholesterol (mg/dL), serum uric acid (mg/dL), blood glucose (mg/dL), serum cholinesterase (IU/L), and serum fibrinogen (mg/dL) levels. Cholesterol level was measured using the CHOD-POD method, glucose level was measured using the GOD-POD method, cholinesterase level was measured using the Ellman method, and fibrinogen level was measured using the Clauss method.

The data was presented as total mean for numerical data and total frequency for nominal or ordinal data. Numerical data was analyzed using an independent *t*-test or Mann–Whitney test. Ordinal and nominal data were analyzed using the Chi-square test. Correlation analysis between serum cholinesterase level and other variables was performed using Pearson or Spearman correlation test for numerical dependent variables.

RESULTS

Of the 106 farmers, 31 farmers (29.2%) were categorized in organophosphate group. The characteristics of the study subjects are presented in Table 1. There were no significant differences in terms of sex, age, years of study, and duration of work between farmers in the organophosphate versus non-organophosphate groups. In physical examination and medical-related habits, there were no significant differences in body mass index, measured blood pressure, and smoking habits between the two groups. The farmers' personal protective equipment score as well as their knowledge towards pesticides were not statistically significant between organophosphate and non-organophosphate groups. Furthermore, the blood markers for stroke risk factors in this case, the measurement of cholesterol, uric acid, and blood glucose levels showed no significant difference between organophosphate and non-organophosphate groups. However, serum fibrinogen levels were significantly different between the two groups. The results showed significantly higher serum fibrinogen levels in the organophosphate group (292.29 ± 67.56 mg/dL) compared to the non-organophosphate group (255.24 ± 38.90 mg/dL), $P < 0.05$.

Table 1: Basic characteristics of the subjects (n=106).

Variables	Total	Organophosphate	Non-organophosphate	*P*
Numbers, *n* (%)	106 (100)	31 (29.2)	75 (70.8)	-
Age, mean (SD, year)	52.92 (13.5)	51.71 (10.1)	53.41 (14.67)	0.492
Sex, *n* (%)				
Male	71 (66.9)	19 (17.8)	52 (49.1)	0.423
Female	35 (33.1)	12 (11.4)	23 (21.7)	
Educational years, *n* (%)				
0–5 years	20 (18.8)	8 (7.5)	12 (11.3)	0.474
6–9 years	76 (71.7)	20 (18.9)	56 (52.8)	
>10 years	9 (8.5)	3 (2.8)	6 (5.7)	
Working years, mean (SD, year)	27.39 (15.2)	22.61 (12.38)	29.57 (16.04)	0.055
Body mass index, mean (SD, kg/m^2)	23.52 (4.01)	23.95 (3.87)	23.33 (4.07)	0.414
Smoking, *n* (%)	43 (40.6)	9 (8.5)	34 (32.1)	0.097
Blood pressure, mean (SD, mmHg)				
Systolic	136.70 (25.92)	137.1 (26.55)	136.5 (25.84)	0.854
Diastolic	80.41 (13.95)	78.67 (13.82)	81.12 (14.03)	0.725
Total cholesterol, mean (SD, mg/dL)	146.8 (53.26)	146.71 (64.06)	146.82 (48.60)	0.444
Uric acid, mean (SD, mg/dL)	5.93 (1.91)	5.93 (2.59)	5.94 (1.57)	0.277
Glucose, mean (SD, mg/dL)	114.39 (29.32)	113.06 (22.94)	114.94 (31.71)	0.958
Cholinesterase, mean (SD, IU/L)	8.57 (1.84)	8.25 (1.48)	8.70 (1.96)	0.593
Fibrinogen, mean (SD, mg/dL)	266.07 (51.55)	292.29 (67.56)	255.24 (38.90)	0.026*
Personal protective equipment score, mean (SD)	46.15 (20.39)	48.70 (17.78)	44.95 (21.53)	0.446
Organophosphate knowledge score, mean (SD)	37.31 (18.43)	38.69 (17.4)	36.68 (18.97)	0.547

*P is considered significant if P<0.05. SD: Standard deviation

We tried to elaborate on whether serum cholinesterase level was related to the physical and metabolic profiles of farmers in organophosphate versus non-organophosphate groups. Using Spearman analysis, we found no significant correlation between serum cholinesterase level with physical profiles such as sex, body mass index, and blood pressure as well as serum markers of stroke risk factors such as blood glucose level, serum cholesterol level, serum fibrinogen level, and serum uric acid level. The significant correlation was found only between serum cholinesterase level and age ($P < 0.05$). The results showed that older subjects had significantly lower serum cholinesterase levels.

The same statistical analyses were performed on serum fibrinogen levels to see whether any physical and metabolic profiles of farmers were significantly correlated with serum fibrinogen levels. The results showed that no other parameters were significantly correlated with serum fibrinogen level ($P > 0.05$). Further multivariate analysis using linear regression showed that organophosphate exposure independently increased the serum fibrinogen level ($P < 0.05$).

DISCUSSION

Our study showed that out of 106 farmers in Seloprojo Village, Ngablak District, Magelang Regency, Central Java Province, Indonesia, who were recruited as the study subjects, 29.2% used organophosphate for pesticides. This organophosphate exposure was independent and significantly caused increased serum fibrinogen levels in the organophosphate group of farmers. Our results supported a previous study by Madani *et al.* that reported increased serum fibrinogen levels in farmers, who had pesticide exposure.[5] Unlike the aforementioned report, our results did not show a significant association between serum fibrinogen level with the personal protection equipment used by farmers and the duration of pesticide exposure.

There has not been an established pathological mechanism for the increased serum fibrinogen level in people, who are exposed to pesticides. Pesticide exposure in high concentrations may cause inflammation and induce fibrinogen secretion from the liver.[5]

An interesting finding in our study was no significant correlation between serum fibrinogen level and serum cholinesterase level. This can be explained that cholinesterase block is not the main mechanism in the inflammation process that may cause an increase in fibrinogen release into the bloodstream. Other reports also proposed that there is an undetermined mechanism other than the decrease of serum cholinesterase level that may cause an abundant release of proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and reactive oxygen species.[7] Therefore, it could be inferred that chronic organophosphate intoxication could cause vascular disturbances and neuropsychological disorders through pathological inflammatory pathways and increased fibrinogen levels.

There was no significant relationship between serum cholinesterase level with blood glucose level, serum cholesterol level, serum uric acid level, hypertension, and body mass index. Some contradictions were found in previous reports regarding the relationship between organophosphate exposure with blood glucose levels. Some reports found that organophosphate exposure may increase the risk of diabetes mellitus incidence whereas other reports found that low blood glucose level was not correlated with high organophosphate exposure.[8] A report from other regions in Indonesia also found that there was no relationship between hypertension with the dose of pesticide, working duration, and the timing of pesticide use.[9] A study by Pothu *et al.* in India showed that there was a significant increase in serum cholesterol, triglyceride, and low-density lipoprotein (LDL)levels as well as a decrease in serum high-density lipoprotein (HDL) levels in the group of people exposed to organophosphate.[10]

Despite being the first study to report the relationship between organophosphate exposure and fibrinogen level in Indonesia, we realized that there were some limitations in our current study, particularly in determining the organophosphate exposure detail. The organophosphate exposure was determined by interviews with the study participants. Furthermore, the pesticide dosage used by the farmers in our study was not measured accurately using a certain measuring scale. In further study, it may be considered to check the organophosphate biomarker such as the urinary level of dialkyl phosphate and the degradation product of organophosphate.

CONCLUSION

Of all biomarkers of stroke risk factors that were studied, there was a significant increase in the serum fibrinogen level of farmers, who had organophosphate exposure in Seloprojo Village, Ngablak District, Magelang Regency, Central Java Province, Indonesia. Increased serum fibrinogen levels may in turn raise the incidence of vascular events.

Ethical approval

This study was approved by the Ethical Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, Ref: KE/FK/0424/EC/2018

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consents.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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