DOI: 10.14260/jemds/2015/1456

ORIGINAL ARTICLE

PATTERN AND SEVERITY OF DIASTOLIC DYSFUNCTION IN ORGANOPHOSPHORUS COMPOUND POISONING PATIENTS IN RELATION TO PLASMA CHOLINESTERASE (PChE) LEVEL IN RURAL POPULATION IN SOUTH INDIA

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HOW TO CITE THIS ARTICLE:
Prashant S. Sidmal, Mallikarjun H. P, K. C. Shekarappa, Prashanthkumar B. G, Umesh Babu R. "Pattern and Severity of Diastolic Dysfunction in Organophosphorus Compound Poisoning Patients in Relation To Plasma Cholinesterase (PChE) Level in Rural Population in South India". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 58, July 20; Page: 10066-10076, DOI: 10.14260/jemds/2015/1456

ABSTRACT: BACKGROUND: Organophosphorus (OP) poisoning is a major public health problem in developing world. OP pesticides inhibit carboxylic esterase enzymes including plasma cholinesterase (PChE). Clinical manifestations following OP poisoning can be associated with the extent of decrease of PChE. This study was designed to investigate the relevance of diastolic function of the heart, severity of diastolic dysfunction and the reversibility of dysfunction in organophosphorus compound poisoning patients in relation to plasma cholinesterase (PChE) levels with the treatment. **MATERIALS AND METHODS:** 76 patients admitted with organophosphorus compound poisoning were evaluated for diastolic dysfunction by echocardiography. Clinical features and the nature of compound involved were recorded. Severity of diastolic dysfunction was assessed. Cholinesterase levels were assessed. Initially there was worsening of diastolic function. As the treatment progressed, there was improvement in the pattern of diastolic dysfunction with the corresponding improvement in cholinesterase level and clinical improvement. This was a cross-sectional study which was conducted from 1st January 2014 to February 2015. **RESULTS:** In total, mean age of patients were 31.2 (range: 19-46) years. Majority of patients were females (68.4%), and agricultural workers (75%). Main clinical findings at the time of admission were congested conjunctiva (83%), pin point pupil (89%), lacrimation (78%), vomiting (69%), non-reactive pupil (85%), respiratory distress (65%) and abdominal pain (45%). Mean (SD) PChE at 6 hours post-exposure was 3242.6 IU/L. At presentation, cyanosis, muscle weakness, convulsion, respiratory distress and fasciculation were related to cases with >75%reduction of PChE, while, constricted and nonreactive pupil, lacrimation and congested conjunctivae were related to cases with 50-75% reduction and abdominal pain, dryness of conjunctiva, vomiting and diarrhea were related to <50% reduction. 11.8% of patients had normal diastolic function. 88.1% patients were found to have diastolic dysfunction. 15.7% had grade I diastolic dysfunction which persisted in same level throughout treatment. In 72.3 % patients there was gradual worsening of diastolic function. With the treatment there was gradual improvement in diastolic function from grade III to grade I. At the end of 5 days, 19.7% patients had complete reversal of dysfunction. 68.4% patients had persistent mild dysfunction even at the time of discharge. **CONCLUSIONS:** Patchy myocardial involvement as a result of direct cardiac toxicity could be one of the factors responsible for cardiac complications. Continuous cardiac monitoring should be undertaken to detect dynamic cardiac changes. These findings can assist health professionals to better evaluate patients' prognosis and improve their treatment plan.

KEYWORDS: Organophosphorus compound, Diastolic dysfunction, Plasma cholinesterase (PChE).

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INTRODUCTION: Organophosphorus (OP) compounds have been employed as pesticides, petroleum additives and chemical warfare nerve agents. The organophosphates have been used as pesticides for more than 50 years and are still used in most developing countries.[1] For the first time, organophosphates were synthesized by von Hoffman. In 1873, he synthesized methyl phosphorus chloride, which led to the synthesis of a number of insecticides. The OP warfare nerve agents, (Commonly called "nerve agents") are much more toxic than pesticides. The commonly used OP insecticides are acephate, anilophos, chlorpyrifos, dichlorvos, diazinon, dimethoate, fenitrothion, methyl parathion, monocrotophos, phenthoate, phorate, pirimiphos, quinalphos, temephos, etc. The replacement of an oxygen atom in the organophosphorus structure by sulfur leads to the formation of organothiophosphorus compounds such as malathion and parathion, which have a lower lethal potential but in vivo metabolization to the oxon metabolite enhances their toxicity.

Since first described as a problem in India over 40 years ago,[1] the problem has continued and clearly increased with India and Sri Lanka being the countries with the highest number of cases.[2] Pesticide poisoning is a major public health problem in developing world.[3,4] Millions of people are exposed to danger of hazardous occupational practices and unsafe storage of pesticides. [5] Organophosphorus pesticides poisoning can result from occupational, accidental or intentional exposure. However, it is deliberate self-poisoning which causes the great majority of deaths and places immense strain on hospital services.[6,7] According to a World Health Organization report, three million cases of pesticide poisoning occur annually worldwide and most of them are in Asia which at least half of them are due to organophosphorus (OP) poisoning.[8,9] They are estimated to cause 300,000 fatalities annually.

OP compounds are amongst the most common poisons used for deliberate self-poisoning in India and other parts of the world[10-15] In many reports from India, rate of suicidal poisoning with OP compounds ranges from 10.3to 43.8%.[11,16,17] Among OP poisoned patients in India, hospital mortality rate is reported to be as high as 20-70%.[18,19]

Being predominantly an agricultural country, OP compounds are used abundantly for farming in India. Hence, access to these hazardous chemical substances is easy. OP pesticides inhibit carboxylic esterase enzymes including acetyl cholinesterase (AChE) and plasma cholinesterase (PChE). AChE can be found in erythrocytes, nervous tissue and skeletal muscles, while PChE can be found in plasma, liver, heart, pancreas and brain. Most of clinical manifestations associated with exposure to OP compounds have been attributed to inhibition of these enzymes.[20]

Diastolic filling consists of two parts normally: rapid, early diastolic (active) relaxation and late diastolic (passive) filling. The first phase depends on the rate of ventricular relaxation, elastic ventricular recoil, the atrio-ventricular pressure gradient, and the passive elastic features of the left atrium and ventricle.[21,22] The second phase formed on the basis of the strength of left atrial contraction and the stiffness of the left ventricle. Diastolic dysfunction occurs when the passive elastic traits of the myocardium are reduced due to increased myocardial mass and changes in the extracellular collagen secondarily.[23]

This leads to stiffening and hypertrophy of the left ventricle with decreased compliance and higher diastolic pressures at each diastolic volume. So, relatively small increases in intravascular volume can lead to elevations in diastolic pressures. Shifting this pressure into the left atrium and pulmonary venous system can lead to pulmonary edema.[23-26] Ventricular diastolic compliance and diastolic function can be assessed by measuring the velocity of blood flow from the left atrium to the left ventricle during early diastole (the E wave) and late diastole (the A wave) and calculating the E/A

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ratio by using the Doppler echocardiography. In other words, determinants of a diastolic dysfunction on a Doppler echocardiogram are decreased E/A ratio, the ratio of early to late (Atrial) phases of ventricular filling and delayed early diastolic trans-mitral filling with prolonged deceleration and isovolumetric relaxation times.[27]

Diastolic dysfunction can be graded as follows according to the diastolic filling pattern (As shown in figure 1).

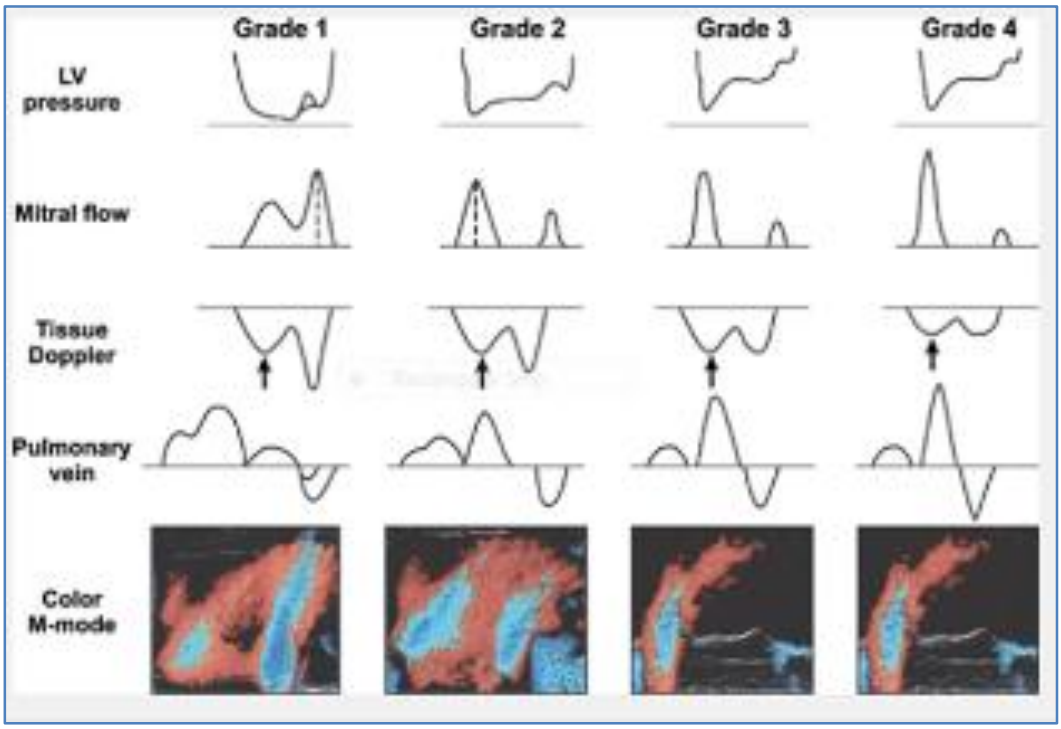

Fig. 1: Grading of diastolic dysfunction

Abnormal left ventricular (LV) filling patterns (Grades 1 to 4). Grading of diastolic dysfunction and filling pattern based on mitral inflow, mitral annulus velocity, pulmonary vein velocity, and color M-mode of mitral inflow. Arrow, Reduced early diastolic velocity (E') of mitral annulus in all stages of diastolic dysfunction (Courtesy Echo Manual, The, 3rd Edition, Oh, Jae K.; Seward, James B.; Tajik, A. Jamil).

Grade 1 = Impaired relaxation pattern with normal filling pressure.
Grade 2 = Pseudonormalized pattern.
Grade 3 = Reversible restrictive pattern.
Grade 4 = Irreversible restrictive pattern.

METHODS: This study was conducted in a tertiary care center in southern part of India from 1st January 2014 to February 2015 after taking approval from ethical committee.

76 patients with definitive diagnosis of OP poisoning were enrolled. Exclusion criteria were liver dysfunction, malnutrition, chronic infections, hypersensitivity reaction, pregnancy, age of more than 60 years and being on medications including codeine and morphine.

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Each patient was assessed according to severity of OP Poisoning. Patients who had manifestations suggestive of severe poisoning were assessed and ventilatory support was administered for them if they had any of the following signs: 1) Apnea 2) Hypoventilation 3) Persistent cyanosis in spite of O2 supplementation 4) Persistent tachypnea or respiratory rate >24/minute 5) Persistent SpO2 <90% with oxygen supplementation 6) Active involvement of accessory muscles of respiration. Table 1 shows severity of OP poisoning.

Grade	Plasma Cholinesterase level	Symptoms	Signs
Mild	<10%	Dizziness, anxiety, headache, tightness, of breath	Rhinorrhea, sweating, salivation, nausea, weakness, coughing, lacrimation, mild bradycardia, hypotension
Moderate	10-50%	Restlessness, confusion, dyspnea, disorientation, abdominal pain, vomiting, diarrhea, drowsiness,	Pallor, miosis/ mydraisis, bradycardia, hypotension, muscle twitching, fasciculation, respiratory depression, bronchorrhea, bronchospasm,
Severe	<50%		Convulsions, respiratory depression, pulmonary edema, flaccid paralysis, involuntary micturition/ defecation, cyanosis, loss of consciousness, coma, hypersecretion and apnea

Table 1: Grading of clinical severity of Organophosphorus compound poisoning

5-mL of intravenous blood was collected from each patient under strict aseptic precautions and analyzed for PChE level. Day 5th on treatment was selected as it has been considered to be the average time required for effect of pralidoxime to eliminate respiratory distress and need for mechanical ventilation. The PChE level was measured using Dimension Clinical Chemistry System (E.I. Dupont De). The normal values of PChE range from 5100 to 11700 with mean (SD) of 8440 IU/L.[28] Based on Proudfoot classification, mild OP toxicity is defined as less than 10% reduction of PChE, moderate toxicity as 10-50% reduction and severe toxicity as >50% of reduction. In keeping with this definition, 4590-5100 IU/L PChE can be considered as mild, 2550-4590 IU/L as moderate and less than 2550 IU/L as severe toxicity. Mean and standard deviation (SD) were calculated using Statistical Package of Social Sciences (SPSS Inc., Chicago, IL, USA).

Electrocardiograph: A12-lead surface EGG was obtained from all subjects. The ECG was recorded at a paper speed of 50mm/s and was analyzed for abnormalities.

Echocardiography: From the time of arrival to the hospital till the day of discharge, diastolic function of the heart was assessed and recorded. Echocardiographic studies were performed using a HDI 3000 (Philips ATL, Bothell, WA, USA) equipped with 2 to 4 MHz probes allowing M-mode, colour Doppler, two dimensional, and pulsed Doppler measurements. Echocardiography was performed

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according to the guidelines of American Society of Echocardiography. Mitral inflow patterns: - The normal E/A ratio is between 1 and 2.

Grade 1 Diastolic Dysfunction (Impaired Myocardial Relaxation): The E/A ratio is < 1, with a prolonged deceleration time (Dct) (>240ms). In the tissue doppler assessment, e' is also reduced with a resultant E/e' ratio (medial) <8, suggesting a normal LA pressure. The D wave of the pulmonary venous inflow is smaller than the S wave and the AR wave is normal.

Grade 2 Diastolic Dysfunction (Pseudonormalized Pattern): When diastolic LV function deteriorates, LV compliance progressively decreases and there is an increase of LA pressure and the diastolic filling pressure. The transmitral E wave velocity progressively increases and the Dct decreases. As it does so, it goes through a phase that resembles a normal filling pattern. The E/A ratio is between 1 and 2 and the Dct between 160 and 240ms. This pseudo-normal pattern is a transition pattern from impaired relaxation to restrictive filling and is a result of a moderately increased LA pressure superimposed on a relaxation abnormality. The following clues help distinguish this from a normal filling pattern E/e' ratio (medial) >15. Pulmonary venous flow AR >25cm/sec and longer than transmitral A wave.

Grade 3 and 4 Diastolic Dysfunction (Restrictive Pattern): With more severe diastolic dysfunction, LV compliance reduces and LA pressures rise. The low compliance of the LV causes a rapid increase in the early LV pressure and a shortened inflow and DT. The E/A ratio is > 2. Dct is < 160ms. The high LA pressure manifests as a E/e' ratio >15 at the medial annulus. Forward diastolic pulmonary vein flow stops in mid-late diastole and during atrial contraction there is a significant flow reversal resulting in a prolonged AR. A reversal to grade 1 or 2 on reducing the preload by performing Valsalva manouvre or administering nitroglycerine suggests reversibility of the cardiac restriction and is termed grade 3. Diastolic filling should be graded as irreversible (grade 4) in the absence of such a reversal.

RESULTS: Socio-Demographic: In total, mean age of patients were 31.2 (Range: 19-46) years. Majority of patients were females (n=52, 68.4 %), and agricultural workers (75%). Monocrotophos, a highly hazardous OP compound, was the most common used poison among the patients (64%).

Clinical and Laboratory Findings: Main clinical findings at the time of admission were congested conjunctiva (83%), pin point pupil (89%), lacrimation (78%), vomiting (69%), non-reactive pupil (85%), respiratory distress (65%) and abdominal pain (45%).

Among 47 patients with respiratory distress, 36 patients required ventilator support. The average time taken for initiating active weaning was 4.6days post-admission in the Intensive Care Unit. Mean (SD) PChE at 6 hours post-exposure was 3833.6 IU/L. PChE level then decreased to 2126.6 at 6 to 12hours post-exposure and 1546.6 at 12 to 24hours post-exposure. At 24 to 48 hours post exposure mean PChE started to rise to 2167.9. After 5 days of treatment, PChE level reached a mean of 9457. 9 (Figure 2). At presentation, 62 patients (91%) had PChE values of less than 5000 IU/L. In addition, in over 45% of patients, PChE suppressed to less than 2000 IU/L (Severe toxicity).

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Fig. 2: Mean Plasma cholinesterase levels in patients with organ phosphorous poisoning in different times of sampling post-admission.

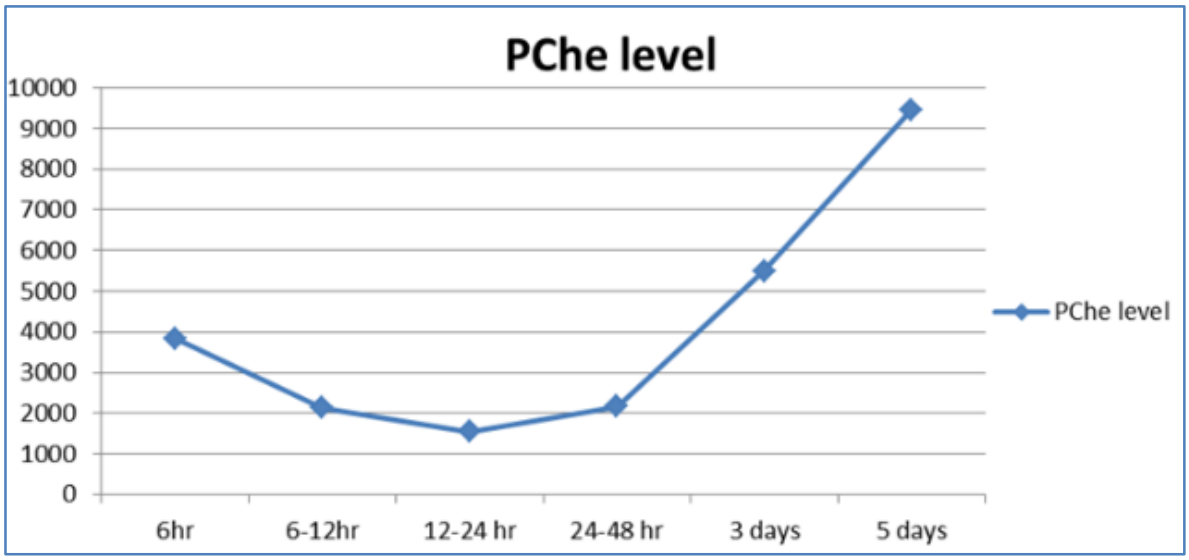

Fig. 2

Relevance of Plasma Cholinesterase Levels: Patients who died had the lowest mean PChE level on first day (1144.2). Among survived patients, those who required ventilator support had the lowest PChE (1256.7) on first day. Subsequently, in the cases presented with muscle weakness, convulsion, respiratory distress and fasciculation, mean PChE on first day was very low as it was reduced to less than 1500. (Severe toxicity). In addition, patients with muscle weakness and fasciculation had the lowest blood oxygen saturation (SpO2<70%) on first day, indicating severe respiratory distress. Death was mostly observed among patients who had respiratory distress. Overall mortality was within the first two days.

Diastolic Dysfunction Assessment: Nine patients (11.8%) had normal diastolic function. 67 patients (88.1%) were found to have diastolic dysfunction. 12 patients (15.7%) had grade I diastolic dysfunction which persisted in same level throughout treatment. In 55 patients (72.3%) there was gradual worsening of diastolic function. At 6 hours post-exposure, these patients had grade I diastolic dysfunction. Later it worsened to grade II at 6 to 12 hours post-exposure and to grade III at 12 to 24 hours post-exposure. At 24 to 48 hours post exposure diastolic dysfunction persisted at grade III. After 5 days of treatment, there was improvement in diastolic dysfunction, with gradual improvement from grade III to grade II and later to grade I (Figure 3). Fifteen patients (19.7%) had complete reversal of dysfunction. Fifty two patients (68.4%) had persistent mild dysfunction even at the time of discharge. (Table 2)

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Fig. 3: Pattern and severity of diastolic dysfunction in organophosphorus compound poisoning patients.

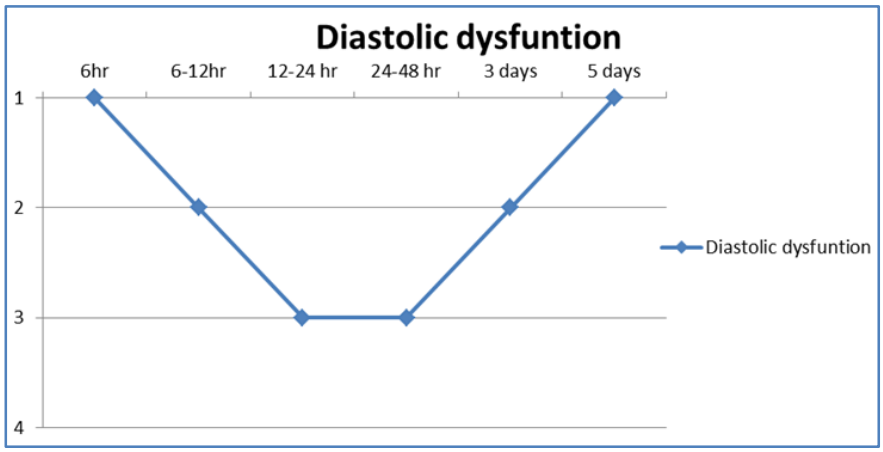

Fig. 3

Gender	Normal function		Persistent Grade I dysfunction		Progression to Grade II & III dysfunction		
	Number	**%**	**Number**	**%**	**Number**	**%**	**Total**
Male	5	6.5%	5	6.5%	14	18.4%	24
Female	4	5.2%	7	9.2%	41	53.9%	52
Total	**9**	**11.8%**	**12**	**15.7%**	**55**	**72.3%**	**76**

Table 2: Distribution of diastolic dysfunction by gender

Sinus tachycardia was the most common electrocardiographic abnormality. The others were corrected QT interval prolongation, ST-T changes, U waves, and ventricular premature contractions.

DISCUSSION: OP poisoning is a major health problem worldwide, especially in developing countries with millions of victims and deaths occurring each year. Determination of AChE and PChE level in blood has remained as a mainstay for the fast initial screening of acute OP exposure which helps healthcare professionals to establish early diagnosis and immediate treatment plan.[29] However, it has been believed that these tests lack sensitivity and specificity, and additionally they might not be related to severity of poisoning.[29] In this respect, Aygun et al. showed that PChE level is useful in diagnosis of OP poisoning in acute phase but it is not correlated to severity of poisoning and also morbidity and mortality.[30] Conversely, Goswamy et al. demonstrated that apart from clinical indicators, low PChE levels were of greatest predictive value in OP poisoning.[31]

In this study, we found that cyanosis, muscle weakness, convulsion, respiratory distress and fasciculation were linked to very low PChE levels. Moreover, we found that as PChE level falls, the O2 saturation decreases and leads to respiratory distress. This can be explained by the fact that mitochondria are the target of OP compounds.[32] Therefore, a more severe OP poisoning which shows itself with lower PChE levels is associated with cellular hypoxia and subsequently severer life-threatening manifestations. Similarly, Kar in 2006 and Tsao et al. in 1990 showed that fatal outcomes

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following OP poisoning were associated with lower PChE levels.[33,34] In addition, they found that all deceased patients had respiratory failure. In this regard, it has been ascertained that the essential cause of death in OP poisoning is respiratory failure which is due to weakness of the respiratory muscles, paralysis of the respiratory centre, bronchospasm and increased bronchial secretion.[35]

Likewise, Chen et al. showed that low PChE activity with non-rising trend within 48 hours of OP poisoning was associated with higher mortality.[36] Moreover, Eddleston et al. revealed that PChE activity can predict death based on the formula of OP compound ingested.[37]

Diastolic dysfunction is a complex process that arises from numerous interrelated contributing factors such as pressure variations in the ventricle, cardiac preload and afterload, and ventricular relaxation and compliance. The increased circulating blood volume, found in patient with OP compound poisoning, leads to a high cardiac preload and decreased peripheral vascular resistance with low cardiac afterload. The alteration in the diastolic function is likely due to an impaired ventricular relaxation. Diastolic dysfunction could be due to the stiffness of the ventricular wall.

In this study, there was progressive worsening of diastolic function. Later with the treatment there was reversal of dysfunction. In this study, diastolic dysfunction in women was significantly more than men (P= 0.004). Similarly, in the study of Redfield et al. they showed that heart failure with normal ejection fraction in any ages is more frequent in women rather than men.[38] So, it could be concluded that the result may be due to the differences of sex hormones in each gender. In our study, diastolic dysfunction was increased significantly by the exposure to OP compounds.

The presence of subclinical myocardial disease with cardiac dysfunction and decreased E/A ratio could be emphasized when patients' cardiac status will be improved by proper treatment.

LIMITATIONS: Although in this study we tried to identify the relevance of mean PChE level with each clinical manifestation, overlapping of features were present in some cases which can reduce the value of our findings. Therefore, to clarify the controversies, further studies with larger samples are recommended while the amount of OP compound consumed is strictly noted. Furthermore, Eddleston et al. proposed that predicting death with PChE level is possible when the ingested OP compound is known.[37] However, in this study, we did not separate the results and outcomes based on the OP poison formula. Long term follow-up after discharge is needed to access the improvement of diastolic dysfunction.

CONCLUSION: A relative relationship between PChE level, diastolic dysfunction and clinical manifestations and outcomes was found. These findings can assist health professionals to better evaluate patient's prognosis and improve their treatment plan.

Patchy myocardial involvement as a result of direct cardiac toxicity could be one of the factors responsible for cardiac complications. Cardiac complications usually occur during the first hour after exposure. Hypoxemia, electrolyte derangements and acidosis are major predisposing factors for the development of these complications. Intensive supportive treatment, meticulous respiratory care and administration of atropine in adequate doses vary early in the course of the illness will reduce the mortality.

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DOI: 10.14260/jemds/2015/1456

ORIGINAL ARTICLE

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FINANCIAL OR OTHER COMPETING INTERESTS: None

Date of Submission: 30/06/2015.
Date of Peer Review: 01/07/2015.
Date of Acceptance: 14/07/2015.
Date of Publishing: 17/07/2015.