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"A Study on Serum Magnesium Level in Organ phosphorus Poisoning and Correlation with Clinical Severity and Its Prognostic Significance"

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Abstract : Introduction*: Organophosphorus chemicals (OPC) are the pesticides most often involved in serious human poisoning. Actually the OPC poisoning is a menace to the human race both as a weapon of mass destruction and pesticide of self- harm.* ***Background:*** *Treatment of intoxication with OPCs conventionally involves atropine for reduction of muscarinic signs and oximes for reactivation of enzyme acetylcholinesterase (AChE). In spite of good care and treatment, the mortality about 19% still persists in our toxicology department , that needs to search for newer predictor and treatment of OPC poisoning. So, serum Magnesium levels were taken for our study purpose. O****bjective****: To correlate the severity of OPC poisoning based on Peradeniya OPC poisoning (POP) scale with serum magnesium levels and with other complications of OPC poisoning.* ***Methods****: cross sectional, prospective study was done at Institute of internal medicine Madras medical college and Rajiv Gandhi government general hospital, Chennai from august 2016 to June 2017among the patients admitted for OPC poisoning.* ***Results:*** *total of 60 patients were included in our study with female predominance of 31. Mean age group 29 ± 9.8 years. With POP scaling mild cases (n=22) , moderate (n=23) and severity (n=15)and mean magnesium values were correlated with clinical severity and outcomes. It is found that clinical severity, duration of hospital stays, Coma stage, intermediate syndrome , arrhythmias, need for mechanical ventilation and death were correlated with decreased serum magnesium levels (p= 0.7) and Renal failure and seizures were not correlated.*

Keywords *- OPC – organophosphorus compounds, POP- peradeniya OPC poisoning, AchE- acetylcholine esterase*

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I. Introduction

Agriculture constitutes the major component of Indian economy. Pesticides are major component of agricultural industry. Organophosphorus compounds (OPC) have been used as both domestic and industrial pesticides. Acute pesticide poisoning is an important cause of morbidity and mortality worldwide. It has been estimated that around three million severe cases of acute pesticide poisonings occur each year with about 220000 deaths. It is estimated that 95% of fatal pesticide poisonings occur in developing countries [(1)]. The easy availability of pesticides makes them a popular method of self-harm. [(2)]

OPC are a diverse group of chemicals used as pesticides. They have been first synthesized by Lassaigne during early 1800 on observing the reaction of alcohol with phosphoric acid. Lange in berlin investigated the use of these chemicals as pesticides. Germans used it as chemical warfare agents during World war II (i.e. tabun, sarin, soman,etc.). Jamaican Jinger Palsy incident in 1930 due to suicidal and accidental exposure to OPC led to probe into its mechanism. Mass poisoning happened in 2005, following ethion contaminated food in India [(3)]. In 1955, Davies introduced Oximes and its usefulness in OPC poisoning.

OPC are basically the esters of Phosphoric acid which terminal oxygen is connected to phosphorus by a double bond, whereas two lipophilic groups and leaving a group are connected to phosphorus by a single bond, which is the principal metabolite for species identification(5). It can be absorbed percutaneously and also when ingested, inhaled and injected. These chemicals equally distributed in all tissues but predominantly in liver and kidneys. Plasma half-life ranges from few minutes to few hours depending upon the type of compounds and route of exposure(5). Metabolism occurs either by oxidation, hydrolysis by esterases or by glutathione reduction. 80 -90% of compounds eliminated by urinary or fecal excretion. Most of agents show symptoms and signs within six to ten hours of exposure with exception of fat soluble compounds where it may take several days to weeks.

Acetylcholine (Ach) is the neurotransmitter in central and peripheral nervous system at all postganglionic parasympathetic nerve endings, at synapses of both sympathetic and parasympathetic ganglia and also at skeletal muscle myoneural junction. Acetyl Cholinesterase (AchE) is an enzyme localized in central nervous system in various organs and glands which hydrolyses acetylcholine into acetic acid and choline. AchE is present in two forms – 1. True AchE : found in tissues and erythrocytes . 2. Pseudo AchE: found in serum and liver(5).

OPC are the irreversible inhibitors of AchE enzyme. In the presence of OPC, the acetylcholine – AchE complex becomes phosphorylated instead of getting acetylated. Once the enzyme becomes phosphorylated, its conversion to free enzyme and acetic acid and choline becomes very slow. Non availability of free enzyme leads to excess acetylcholine in the synapse and neuromuscular junction leading onto toxic clinical consequences. The reactivation of AchE may occur spontaneously or may be enhanced by Oximes(6,7).

Gastrointestinal symptoms like vomiting, diarrhea and abdominal cramps are the first to occur after oral ingestion. Respiratory tract integrity is compromised by excessive secretions. Paralysis of respiratory muscles occurs due to nicotinic effects. Central nervous system depression leads to respiratory arrest. Cardiac manifestations are often the cause for serious complications and fatality. Mechanism may be due to direct toxicity on the myocardium or due to other contributory factors like hemodynamic alterations, acidosis, hypoxia,hypomagnesemia etc.

Neurological manifestations are -Type 1 paralysis or Acute cholinergic crisis: it is seen in initial phase of exposure characterized by muscle fasciculation, weakness, cramps etc. may require ventilator support. This phase usually lasts for 48 – 72 hours([8,9,10]). Type 2 paralysis or Intermediate syndrome([11]): it usually develops after 12 – 96 hours of exposure. The proposed mechanism were - different susceptibility of various cholinergic receptors, muscle necrosis, prolonged AchE inhibition. This phase is characterized by weakness of neck muscles and motor cranial nerves like respiratory muscles, proximal limb muscles and cranial nerves like III,IV and VI with sparing of distal muscle group. This phase lasts for 4- 18days and may require ventilator support.

Normal serum magnesium (Mg) level is 1.7 – 2.1 mg/ dl. Mg is involved in metabolism of proteins, fats, carbohydrates and act as co- factor for the enzyme ATPase. Mg ions interfere with the release of acetylcholine and blocks neurosynaptic transmission. Hypomagnesemia is usually associates with hypokalemia.

Hypomagnesemia causes cardia arrhythmias, convulsions, muscle cramps, depression and generalized weakness like quadriplegia with respiratory muscle weakness. Acute OPC will produce hypomagnesemia due to prolonged nasogastric suction, severe diarrhea, underlying illness like starvation, chronic alcoholism, diabetes mellitus, hyperthyroidism etc.[12,13]

OP components alone account for 80% of pesticide poisoning. In our center, Rajiv Gandhi Government Hospital, Chennai received 340 cases in the year 2017 with mortality rate of 19%, mostly due to respiratory paralysis and mechanical ventilation related complications

II. Objectives

1. To access and categorize the severity of OPC poisoning cases clinically, on admission by Peradeniya Organophoshorus poisoning Scale.
2. To estimate the serum magnesium level on admission in acute OPC poisoning.
3. To correlate the serum magnesium level with clinical severity scoring.
4. To correlate the serum magnesium level with the atropine requirement during the course in hospital.
5. To correlate the serum magnesium level with one or more of complications like respiratory paralysis, intermediate syndrome and the need for mechanical ventilation, acute renal failure , seizures , arrhythmias and coma.

III. Methodology

Study design:
Cross sectional, Human subjects, unicenter, randomized, single-blind prospective study.

Study Centre:
Institute of internal medicine Madras medical college and Rajiv Gandhi government general hospital, Chennai

Study duration:
October 2016 to June 2017 – 9 months

Inclusion criteria:
Confirmed cases of OPC poisoning

Exclusion criteria:

1. Patients with other pesticide poisoning (e.g. organo-carbamates) have been excluded by history and clinical features.
2. Patients with mixed poisoning
3. Patients who had taken compounds with alcohol have been excluded.
4. Patients with known medical illness such as chronic liver disease, myopathy, malignancy, renal failure, autoimmune disease, seizure disorder, coronary artery disease etc.
5. Patients who were on chronic drug usage with statins, steroids, diuretics
6. Pregnant patients were excluded from the study

Sample size:

Total of 60 patients - includes 29 males and 31 females.

IV. Methodology

Patients satisfying above inclusion and exclusion criteria were taken up for study after obtaining consent. Demographic data, history, systemic examination were recorded. Patients were assessed clinically on admission by peradeniya organophosphorus poisoning scales and categorized according to the severity. They were subjected to routine blood investigations like blood sugar, blood urea, liver function test, ECG and ABG. Serum cholinesterase level was estimated by KINETIC CALORIMETRIC METHOD.Serum Magnesium level was estimated by CHLOROPHOSPHONAZO III METHOD.

All the patients admitted were graded with Paradeniya Organophoshporus Poisoning Scale.

Parameters	Criteria	Score
Pupil size	>2 mm	0
	<2mm	1
	Pin point	2
Respiratory rate	< 20/ min	0
	>20 / min	1
	>20/min with central cyanosis	2
Heart rate	>60/min	0
	40 - 60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized/ continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal commands	1
	No response to verbal commands	2
Seizures	Absent	1
	Present	2

Scoring: score 0- 3 mild poisoning, 4-7 moderate poisoning, 8-11 severe poisoning.

All the admitted patients received the routine treatment comprising of gastric lavage, administration of 1 g/kg activated charcoal and serial administration of activated charcoal, bathing with water and soap at least three times a day, appropriate bolus and maintenance doses of atropine (the end-point of atropinization was drying of secretions, flashing, tachycardia and mydriasis), and appropriate doses of oximes (pralidoxime). The starting dose of pralidoxime was 1- 2 g i.v. Additional doses were given in a bolus of 1- 2 g i.v. over 30-60 min every 6- 12 hours according to severity of poisoning. The ideal dose of atropine and pralidoxime was determined by monitoring the clinical condition of the patient and serial assessment of cholinesterase levels over a period of several days.

In our study, among 60 patients, 18% constitute age group of < 20 years, 37% constitute age group of 21- 30 years, 27% 31 – 40 years, > 40 years about 19%. 29 patients consumed <50ml of OPC, 20 patients consumed 51- 100ml and > 100ml by 3 patients , 8 patients found unconscious.Total of 9 patients arrived to hospital within 3 hours of consumption, 37 patients arrived around 4- 7 hours, 12 patients arrived within 10 hours and 2 patients more than 10 horus.

Quantity of amount consumed	Clinical severity based on Peradeniya OPC Poisoning severity scoring			Outcome		P – value
	Mild	Moderate	Severe	Discharge	Death	
< 50 ml	18	09	03	23	0	0.085
50 – 100ml	04	12	08	20	3	
>100 ml	0	02	04	10	4	
Total	22	23	15	53	7	

Clinical severity	Mean Magnesium values (mg/dl)	Duration of hospital stay				Arrhythmias	Coma	Mechanical ventilation	Intermediate syndrome	P - value
		< 7 days	8- 14 days	15 – 21 days	>21 days					
Mild (n = 22)	1.9	22	01	01	0	0	0	1	1	0.079
Moderate (n= 23)	1.64	05	11	05	2	01	1	14	6	
Severe (n= 15)	1.51	0	02	05	7	02	5	13	7	

Clinical severity based POP scoring	**Mean magnesium values (mg/dl)**	**Initial AchE levels**	**Death**	**P - value**
Mild (n= 22)	**1.9**	**2335**	**0**	**0.067**
Moderate (n=23)	**1.64**	**1123**	**3**	
Sever (n = 14)	**1.51**	**899**	**4**	

V. Results

In our series, females (n=31) dominated, probably due to many male patients were excluded due to mixed poison with alcohol. 49 out of 60 cases were below the age group of 40 years with mean age of 28.6±9.8 years. POP scoring was much reliable that it correlated clearly with the duration of hospital stay, development of complications, quantum of exposure and initial magnesium levels. Our results showed that decreased serum magnesium levels correlated with poor outcome in the form of increased atropine requirement(n= 15), duration of hospital stay(n = 22), incidence of intermediate syndrome (n= 14), mechanical ventilation(n = 28) , death(n= 7) with p value (0.07). Renal failure, seizures incidence doesn't't correlate with serum magnesium levels (p = 2.09). it is our opinion from the study that initial reduced serum magnesium level will correlate with poor clinical outcome and intravenous magnesium sulfate may corrects hypomagnesemia in addition to the reduction in Ach release from pre synaptic terminals, thus reducing morbidity and mortality.

VI. Conclusion

1. Peradeniya Organophosphorus Poisoning Scale is the excellent classification system for categorizing the severity of cases with acute organophosphorus poisoning.
2. Serum magnesium levels can be used as the predictor for severity of acute OPC poisoning.

VII. Limitations

1. Only OPC poisoning alone included in this study and even organic- carbamates were not included
2. Most of the patients admitted were taken poison along with alcohol and they were excluded.

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