"STUDY OF LEVELS OF SERUM CREATINE PHOSPHOKINASE AND LIVER ENZYMES AS A PROGNOSTIC INDICATORS IN ACUTE ORGANOPHOSPHORUS POISONING"

By

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DR BANASHANKARI S KOLLUR

LIST OF ABBREVIATIONS

>	–	more than
<	–	less than
2-PAM or P2AM	–	Pralidoxime
AChE	–	Anticholinesterase
Ach	–	Acetyl choline
Acetyl–coA	–	Acetyl coenzyme A
CPK/CK	–	Creatine phosphokinase/Creatine kinase
CK-MB	–	Creatine kinase - myoglobin
CNS	–	Central nervous system
DDT	–	Dicholoro-diphenyl trichloroethane
ECG	–	Electrocardiogram
Fig	–	Figure
GI	–	Gastrointestine system
GCS	–	Glasgow coma scale
Hrs	–	Hours
HupA	–	HuperzineA
IMS	–	Intermediate syndrome
NMJ	–	Neuromuscular junction
No.	–	Number
OP/OPC	–	Organophosphorus compound
OPP	–	Organophosphorus poisoning
PChE	–	Pseudocholinesterase

PNS	–	Peripheral nervous system
PaO2	–	Partial pressure of O2
SChE	–	Serum cholinesterase
TEPP	–	Tetraethyl pyrophosphate
Yrs	–	Years

ABSTRACT

BACKGROUND AND OBJECTIVES:

Poisoning has been found to be a major cause of death or morbidity in the developing world, the common being Organophosphorus (OP) poisoning. Erythrocyte cholinesterase (EchE) and pseudocholinestrase (Butyryl cholinesterase – BchE) are markers used for assessing the severity in OP poisoning but estimation of these are costly and has variable values for different individuals and are not available at all centers. This study was done to estimate levels of serum Creatine Phosphokinase (CPK) and liver enzymes in acute OP poisoning patients and its prognostic significance.

METHODOLOGY:

Patients admitted in SHRI B M PATIL MEDICAL COLLEGE AND RESEARCH HOSPITAL were the study group. 80 patients were included in the study after inclusion and exclusion criteria. Information was collected through a preformed and pre-tested proforma from each patient. Qualifying patients were subjected for detailed history, clinical examination and biochemical examinations. Serum levels of Creatine kinase and Liver enzymes were analysed at the time of admission.

RESULTS: Out of 80 patients recruited for the study, 41 cases (51.3%) were females, and 39 cases (48.8%) were males. Majority of them were in the age group of 21-30 years. More cases of OP poisoning were among agriculturalists 28 (35%) and housewife 21 (28.8%) and among students 15 (18.8%). Malathion was the most common compound used followed by Monocrotphos. 60% had mild, 31.3% had moderate and 8.8% had severe poisoning. There is increase in CK levels in 6 patients who survived with ventilator support and also in 2

patients died with ventilator support which was statistically highly significant ($p<0.013$). Serum liver enzymes were within normal limits.

CONCLUSION: Elevated Creatine kinase is commonly seen in OPC poisoning. High initial serum CPK levels are associated with severe degree of poisoning and are associated with complications and mortality. Serum liver enzymes are not elevated in OP poisoning.

KEY WORDS: OP compound, Creatine kinase, Liver enzymes, respiratory failure.

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INTRODUCTION

Organophosphorus (OP) insecticides are arguably one of the common causes of morbidity and mortality due to poisoning worldwide especially in developing countries like India. The morbidity and mortality depends on the time lag between the exposure and the onset of management.[1] According to the World Health Organization (WHO), 1 million serious unintentional poisonings occur every year and an additional 2 million people are hospitalized for suicide attempts with pesticides. These compounds act by inhibiting the enzyme acetylcholinesterase (AchE) which result in accumulation of acetylcholine at muscarinic and nicotinic receptors producing an array of symptoms principal site being the peripheral nervous system.[2]

Deaths occur due to respiratory failure occurring in one of two distinct clinical syndromes: acute cholinergic respiratory failure or the intermediate syndrome. Delayed failure appears to be due to respiratory muscle weakness but its pathophysiology is unclear.[3]

Patients with acute OP poisoning are usually monitored by using serum AchE level which are expected to fall. It is not specific and does not correlate with the severity of poisoning and cannot be used as a prognostic indicator. There are emerging options for new cheaper and/or easily quantifiable biochemical markers in relation to OP poisoning like Creatine phosphokinase (CPK).[2, 4]

Estimation of CPK is easy and levels are increased both in acute phase and in intermediate syndrome due to muscle fibre necrosis. It has been reported that high serum

CPK levels reflect the magnitude of acute muscle necrosis and is the best and most sensitive indicator of muscle injury.[5, 6]

With increased use of compounds for agricultural and industrial purposes and due to easy access and low cost, they are becoming a major source of health hazard. So it is cardinal to recognize the entire spectrum of symptoms. Identification, risk stratification, early diagnosis and prompt treatment of OP poisoning victims are equally vital.

The definitive and the gold standard method in the diagnosis of OP poisoning is established by demonstrating a decreased cholinesterase in the blood. Serum cholinesterase levels are easier to estimate and are usually decreased after OP poisoning as also reported by previous studies done.

Every now and then case reports on clinical significance of liver enzymes and creatinekinase in acute OP poisoning has been documented but studies in context with clinical significance of liver enzymes and creatinekinase, no large-scale studies were done so far. Hence an effort is done to study its clinical significance of liver enzymes and creatinekinase in OP poisoning.

AIMS AND OBJECTIVES OF THE STUDY

To assess serum Creatinekinase and liver enzymes levels in OP poisoning and its prognostic significance.

REVIEW OF LITERATURE

HISTORICAL ASPECTS:

Organophosphorus (OP) is the general name for organic derivatives of phosphorus. Philipe de Clermont in 1854 was the foremost to publish an account of synthesis of a highly potent compound of the Organophosphorus anticholinesterase (anti-ChE) series, tetraethyl pyrophosphate (TEPP), 10 years before the isolation of physostigmine.[7] Homstead in a later century noted that it was extraordinary how an investigator survived tasting of the compound.[8] In the 1930s a neurological syndrome called Jamaican ginger paralysis was seen in illicit alcohol consumers caused by bootleg whisky contaminated with OP derivative.[9]

Subsequently in 1932, Lange and Kreuger with chance observation discovered the biological activity of OP esters producing a strong cholinergic effect in human beings. Around 1936-37, German scientist Gerhard Schrader also noticed similar effect during his synthetic work and developed a method for TEPP production on a commercial scale. An extensive work by Schrader on these compounds during the world war II lead to the synthesis of around 2000 compounds like parathion, Systox, Tabun, Sarine etc.[10,11]

Upon synthesizing approximately 2000 compounds, Schrader[10] defined the structural requirements for insecticidal (and as learned subsequently, for anti-ChE) activity. One compound in this early series, parathion (a phosphothioate), later became the most widely used insecticide of this class. Organophosphorus compound first came to India in 1951, to be used as an insecticide. In 1962 first Organophosphorus poisoning was reported in India.[12]

The organophosphates have achieved great popularity because of their effectiveness as insecticides and their lack of persistence in the environment. Because of their unstable chemical structure they disintegrate into harmless radicals within 4 days of application, unlike DDT and other Organochlorides they do not persist in body or environment and replaced DDT as insecticide agent of choice.

Creatinekinase (CPK) and Liver enzyme levels were found to be elevated in many acute Organophosphorus poisoning cases. Increase of creatinekinase (CPK) and Liver enzymes in acute OP poisoning cases have also been reported earlier in humans.

Creatinekinase (CK) is involved in energy storage in tissues, primarily muscle during active muscle contraction, adenosine triphosphate (ATP) is used up and creatine phosphate is converted by CK to creatine and ATP. For continuous contraction during periods of rest ATP is converted to creatine phosphate by CK to serve as an energy reservoir. Molecular weight of Creatinekinase is 40 k Da which is mainly seen as a dimer of catalytic subunits, **M** (for muscle) and **B** (for brain) are its subunits and CK1 (BB), CK2 (MB) and CK3 (MM) are its isoenzymes.

Kuntal Bhattacharyya et al[2] conducted a prospective study in 2011 At Medical college, Kolkata, India upon 63 patients of OP poisoning to find out the level of creatinekinase and its prognostic significance. The CPK level was estimated for 61 patients. Two patients (Initial CPK 1138 IU/L & 1086 IU/L) died out of complications during the course of therapy on day 3 & day 5 respectively. It was found that mortality was more in patients with high initial CPK level. Another 3 patients developed

intermediate syndrome on day 3 had initial CPK level 1138 IU/L & concluded serum CPK can be an efficient biomarker in case of acute OP poisoning.

A prospective study done in 121 patients by S.B. Agarwal, V.K. Bhatnagar et al[110] in the year 2007 in B. J. Medical College and Civil Hospital, Ahmadabad India and observed that the levels of serum LDH and CK are significantly increased and more significant increase in levels are seen in patients who are expired due to OP poisoning.

A. Patel, V. Shivgotra & V. Bhatnagar et al[111] in the year 2008 conducted a prospective study in workers engaged in OP insecticide production. A total of 161 workers were included as subjects in this study. There were 40 subjects in control group, 50 subjects in maintenance group and 71 subjects in exposed group. The serum levels of SGOT & SGPT were within normal limits in the maintenance and exposed groups subjects. They did not look for creatinekinase.

A cohort study done in 106 patients in the year 2006 by Antonio F. Hernandez et al[112] and stated that many criteria are used to estimate pesticide exposure and one of them is serum cholinesterase. Their results showed that there is an association of pesticide exposure with changes in increased activity of AST, LDH and decreased activity of amino-oxidase as well as with increase in levels of creatinekinase.

Dilshad A Khan, Mahwish M Bhatti et al[113] Department of Pathology, Army Medical College in 2008 conducted a prospective study on 109 patients and concluded that the activity of butrylcholinesterase was significantly less in farmers who are exposed to pesticides (49 cases) when compared to controls ($P<0.001$) and Plasma biochemical markers such as ALT, AST, CK, LDH and phosphate were significantly high. There is a

significant positive correlation with AST, LDH, ALT in patients who are exposed to pesticides.

Kale BS[116] conducted study at V.G. Shivdare College in April - 2011 they studied total 40 Organophosphorus poisoned patients and 40 controls. Organophosphorus poisoned patients were identified by attending physicians on the basis of symptoms shown by patients. The creatinekinase activity was much increased ($p < 0.01$) in different stages of Organophosphorus poisoning cases as compare to controls. More significant alterations in creatinekinase activity are seen in patients who are died because of impaired cardiac function caused by OP toxicity. They found that in moderate (20 cases) and severe poisoned (13 cases) creatinekinase was more elevated. Study concluded that estimation of creatinekinase may serve as a suitable diagnostic marker for muscular damage in OP poisoning.

Vijaya kumar PG et al[117] conducted a study in Government General Hospital, Chennai in April 2008, analyzed for CK in OP poisoning cases. Results revealed elevation of CK in Grade 2 & 3 acute OP poisoning cases. Grade 1 cases showed a mild increase in CK. Study concluded that increase of CK in acute OP cases is indicating of severity of poisoning and respiratory depression and need for mechanical ventilation.

Prospective observational study was done in 80 patients by Eizadi Mood N[118] et al in the department of Clinical Toxicology Isfahan, Iran and included the patients whose serum CPK level is > 250 IU/L and assessed the severity of poisoning by using Poisoning Severity Score. Based on their admission serum CPK level they categorized into 3 groups- Low, Medium, High groups and around 35% in low group, 29.5% in medium

group, 75% in high group have developed complications or death. They have found that the admission serum CPK levels are used as an important predictor for the outcome of a patients in OP poisoning.

Eun-Jung Kang, Su-Jin Seok, Kwon-Hyun Lee et al[114] found that the CPK activity was significantly high in patients with poisoning and more significant alterations in CPK activity are seen in patients who are died because of impaired cardiac function caused by OP toxicity. Alternative to cholinesterase the estimation of serum CPK level in suspected individual can be used as corroborative diagnostic and prognostic parameter.

ANATOMY AND PHYSIOLOGY OF NEUROMUSCULAR JUNCTION ACETYLCHOLINE:

Acetylcholine (Ach) first synthesized by Bayer in 1867 is a neurotransmitter. It was first recognized as a potent pharmacological substance by Hunt in 1906.

Acetylcholine is produced at

a) All Parasympathetic Postganglionic fibers

b) All Preganglionic neurons

c) Sympathetic postganglionic neurons that innervate sweat glands

d) Sympathetic postganglionic neurons that end on blood vessels in skeletal muscles and produce vasodilatory effect when stimulated.

The Ach is synthesized in the motor terminal nerve endings and stored in vesicles of cholinergic nerve fibers in highly concentrated form till until it is released. The cholinergic nerve terminal releases the Ach into a tissue where it is present only for few seconds to perform its nerve signal transmitter function then its splits into choline and acetate ion and then catalyzed in local connective tissue by an enzyme acetylcholinesterase. The choline which is formed is transported back into terminal nerve endings for the synthesis of new acetylchoine.[13]

$$\text{Choline} + \text{Acetyl-CoA} \xrightarrow{\text{Choline Acetyl Transferase}} \text{Acetylcholine}$$

In axoplasm of nerve terminal about 20% of Ach is present as free Ach and of it around 80% of Ach is present within the vesicles.[13]

There are separate stores of Ach is present within the nerve terminal. Most of the Ach (80%) can be released by nerve impulses (the releasable store) but some cannot (the non-releasable store or stationary store). The releasable store consists of the Ach contained within the vesicles whereas non-releasable is the Ach of the axoplasm. Releasable store is often divided into immediately available and the reserve store.

Ach acts by two receptors: [13]

a) Muscarinic receptors:

Muscarine receptors are present on all effector cells which are stimulated by the postganglionic cholinergic neurons of sympathetic or parasympathetic nervous system.

Actions of acetyl choline at muscarinic receptors are as follows

Site Action

1. **Heart:** Bradycardia, Cardiac arrest, AV block

2**. Blood vessels:** Vasodilatation which in turn causes fall in pressure and flushing

3. **Smooth muscle**

- Gastrointestinal: Increases contraction
- Bronchial: Constriction
- Bladder: Detrusor contraction and sphincter relaxation

4**. Glands:** Increased secretions Sweat, lacrimal, saliva, gastric and tracheobronchial

5. **Eye:** Constriction of circular muscles of iris which causes miosis

b) **Nicotinic receptors:**

Nicotinic receptors are present in autonomic ganglia at the synapses of pre and postganglionic neurons of both the sympathetic and parasympathetic systems.[13]

Actions of acetyl choline at nicotinic receptors are as follows*:*

1. At skeletal muscles it produces twitching and fasciculation.
2. At autonomic ganglia it causes stimulation which in turn causes tachycardia and rise in blood pressure

METABOLISM OF ACETYLCHOLINE:

Junctional acetylcholinesterase is the enzyme responsible for the hydrolysis of Ach in the synaptic cleft. Acetyl cholinesterase is a protein attached to the basement membrane of the muscle and probably also to membranes of the motor end plates and the nerve terminals. Under normal circumstances a molecule of acetylcholine reacts with only one receptor before it is hydrolysed. This arrangement ensures that each Ach molecule only reacts once with the receptor, after which it is rapidly (in < 1msec) hydrolysed.[15]

TYPES OF CHOLINESTERASES:

Two major forms of cholinesterase exist in vertebrates which hydrolyze acetylcholine.[16]

A) SERUM CHOLINESTERASE: (Pseudo cholinesterase or Butyryl Cholinesterase)

Serum cholinesterase is a tetramer of four identical sub-units each containing 574 amino acids with a total weight of approximately 342,000 Daltons. The tetrameric sub-units are held together by two inter chain disulfide bridges and by hydrophobic, non-covalent forces.[17] The enzyme has two active sites, the anionic site acting on positively charged quaternary ammonium groups on the substrate and esteratic site, breaking ester bonds. The enzyme is a glycoprotein synthesized in the liver containing about 24% carbohydrate. It is found in the serum, liver and in CSF in small amounts[18]. The physiological function of enzyme (PchE) is still not known. The half-life of PchE is about 12 days.[19]

B) RBC CHOLINESTERASE: (True, Specific Cholinesterase).

True cholinesterase is also a tetramer of four identical sub-units. The enzyme is a glycoprotein containing about 16% carbohydrate, found in nerves, neuromuscular junctions and erythrocytes. Its physiological function is largely unknown

DECREASED PLASMA CHOLINESTERASE ACTIVITY: is either by genetic defects, physiological variation or iatrogenic.

1) Physiological variations:

-Age - About 50% of normal PchE activity is seen in newborn

- Normal levels of PchE activity is seen at puberty

- In old age (i.e. 75-80 years) the activity is 75% of normal

-During pregnancy PchE activity decreases by 20-30%[20]

2) Disease:

a) Liver disease - PchE activity decreases to 50% in liver cirrhosis and liver metastasis.

b) Renal disease - PchE activity decreases to 30% of normal in renal disease (uraemia) [20]

3) Drugs - Organophosphorus and organocarbamate compounds

- Anti cancer drugs (cyclophosphamide)

- Ecothiophate eye drops

- Bambuterol (bronchodilator)

4) Genetic - Patients with atypical PchE have low PchE activity[20]

Organophosphate and organocarbamate compounds inhibit acetyl cholinesterase by interacting with the enzyme's active site. The inhibited enzyme is unable to metabolize acetyl choline. The resultant excess concentration of acetyl choline produces excessive stimulation of nicotinic and muscarinic receptors leading to manifestation of symptoms of poisoning.

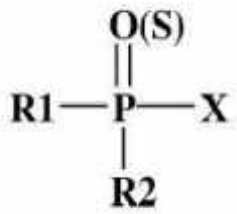
Acetylcholine is inactivated by combination with two sites on the enzyme RBC cholinesterase: Anionic site and Esteratic site.

Anionic site:-Bears a negative charge which attracts the quaternary nitrogen ion (N+) of acetylcholine.

Esteratic site:-Attracts the carboxyl group of Acetylcholine molecule and the esteratic site of the enzyme is acetylated and this results in splitting of choline. The acetyl group in combination with the esteratic site is however immediately removed as a result of combination with water, forming acetic acid. This sets the esteratic site of the enzyme free for further inactivation of acetylcholine.

PHARMACOLOGY:

The Organophosphorus insecticides are a closely related to family of chemicals which differs in its structure. They are usually ester, amide or thiol derivatives of phosphoric or phosphonic acids, the general formula being:



The basic structure consists of phosphorus, which is bound to oxygen (O) by a double bond, R1 and R2 may be alkyl, alkoxy, aryloxy, amido, mercaptan or other groups. X represents the leaving group, a conjugate base of weak acid is found as a halide, cyanide, thiocyanate, phenoxy and thiocholine or carboxylate group. The P=S form is intrinsically more stable and many of the insecticides are manufactured in that

form, which may be converted subsequently in vivo to the biologically active form oxon.[8, 92]

Organophosphorus compounds inhibit enzyme acetyl cholinesterase. The mechanism of inhibition of the enzyme is by reacting with the esteratic site on the acetyl cholinesterase molecule. The bond formed between phosphorus atom and the esteratic site of enzyme is stable and requires hours to weeks for reversal depending on the type of Organophosphorus compound. Phosphorylated enzyme is inhibited because of occupation of its active site. It is incapable of carrying out its normal function of hydrolysing acetyl choline.

This Phosphorylated enzyme can undergo spontaneous hydrolysis or de alkylation. Due to spontaneous hydrolysis active enzyme cholinesterase is released and this is called reactivation. The Phosphorylated enzyme can also undergo dealkylation. Once this occurs, reactivation is impossible. This process is called ageing.[21] Once ageing occurs recovery of cholinesterase activity depends on synthesis of new enzyme by liver which may take days or weeks.

Hence the three independent reactions determine the speed of onset and severity of poisoning i.e.

- Phosphorylation of cholinesterase by Organophosphorus compounds
- Reactivation
- Ageing

Organophosphorus compounds are divided into two series of compounds, alkyl phosphates (direct inhibitors) like malathion and aryl phosphates (indirect inhibitors) like parathion.[7, 22, 23]

Poisoning by direct inhibitors of acetyl cholinesterase presents as an acute cholinergic crisis, they do not develop late type muscular weakness. Response to atropine is rapid. Indirect inhibitors do not develop signs of cholinergic crisis but show persistent fasciculation along with sudden increase in atropine requirement.

The incidence of development of late type of muscle weakness is high. The correlation between the degree of enzyme inhibition and the severity of manifestations is pertinent only in the initial stage of acute poisoning. Inhibition is greater in repeated exposures[24]. Inhibition remains even after recovery from symptoms.[24]

PHARMACOKINETICS:

Most of the organophosphate insecticides are rapidly absorbed by all routes like dermal, respiratory, gastrointestinal and conjunctival. These chemicals are detoxified by cytochrome P450 mediated mono-oxygenases in liver. Metabolism occurs principally by oxidation, hydrolysis by esterase and transfer of a portion of molecule to glutathione. Most of the Organophosphorus compounds are excreted almost entirely as hydrolysis products in the urine. 80-90% elimination occurs within 48 hours. A very small proportion of the Organophosphorus compounds and their active forms Oxons are eliminated unchanged in the urine. Some compounds (fenthion, fenithrothion) are known to persist in the body for longer periods.

TABLE 1: CLASSIFICATION OF INSECTICIDES[25]

ORGANO CHLORINE COMPOUNDS	ORGANOPHOSPHOROUS COMPOUNDS	CARBAMATES
Methoxychlor	Chlorthion	Carbaryl
DDT HCH (BHC)	Diazinon	Aldicarb
Lindane	Dimethoate	Propoxur
Chlordane	EPN	Methomyl
Hepatochlor	Malathion (OMS-1)	Thiodicarb
Dieldrin	Fenthion (OMS-2)	Carbofuran
Aldrin	Methylparathion	Carbosulfan
Dicofol	Parathion	
	Ronnel	
	Trichlorfos	
	Dichlorvos	
	Chlorpyrifos	

TABLE 2: FREQUENTLY ENCOUNTERED ORGANO PHOSPHORUS POISONINGS IN HOSPITAL EMERGENCIES[25]

GENERIC NAME	TRADE NAME
Monocrotophos	Nuvacron, Huvacron,Atom, Azodrin, Balwan, Corophos, unicron
Fenthion	Baytex, Lebaycid, Fenthiosul, Agrocidin
Fenitrothion	Tik-20, Folithion, Agrothion, Vikathion, Sumithion, Fenitrosul-50, Fenicol
Malathion	Finit, Vegfru, malatox ,Himalaya, Agroma, Cythion, Bharat, Celthion, Maladon
Methyl Parathion	Finit, Vegfru, malatox ,Himalaya, Agroma, Cythion, Bharat, Celthion, Maladon
Phosmet	Phosmite
Phorate	Anuphorate, Croton, Dhan, Dhang, Dragnet
Oxydemeton	Hexasystox, Phoratox , Knock out, Hymox, Dhanucytex
Quinalphos	Agroquin, Agroquinol, Bayrusil, Chemlox

TABLE 3: LESS COMMONLY ENCOUNTERED ORGANOPHOSPHORUS POISONINGS[25]

GENERIC NAME	TRADE NAME
Anilofos	Aniloguard,Arozin
Dichlorovas (D.D.V.P)	Agrovan, Bangvas, Sevious, Agro 76 EC, Nuvasul-76, Paradeep, Nuvan
Diazinon	Agroziron, Bazanon, Suzinon, Zionosul-20
Phosphomidon	Bangdon 85WSC, Agromidon 85 WSC, Cildon, Entecron 85, Phamidon, Vimidon, Sudon, Phosul
Chlorfenvinphos	Chlorfenvinphos, Birlane
Dimethoate	Agrodimet-30, Banggor-30Ec, Cropgor-30, Parrydimate, Agromet-30Ec, Hygro-30, Entogar, Paragor-30, Milgor, VikagorDimethoate, KlexDimethoate, Rogar, Ramgor, Tara, Dimex, Sulgor, Paragor, Tagor
Ethion	Force, Ethion, Miticil, Dhan-unit, VegfruFosmite, RP-thion 50 EC, Tafethion, Mit 505, Ethiosul50, RP-Thion EC
Formothion	Anthio, Accothion
Ediphenphos	Hinosan
Chloropyriphos	Coroban20, Agrofilas 20, Gilphos, Hyban20, Chlorofos 20, Ruban 20, Dursban, Tafaban
Acephate	Asataf, Acemil, Agrophate, Starthene, Hythane

CLINICAL MANIFESTATIONS:

The clinical manifestation of OP poisoning depends on the agent, amount and route of entry. More rapid development of symptoms are seen through ingestion and inhalation route than by dermal exposure[26] within 30-90 minutes the symptoms will appear after ingestion and a maximum of 24 hrs in case of compounds which are highly lipophilic and which require metabolic bioactivation.[26]

LOCAL EFFECTS: Before the onset of systemic symptoms the GI symptoms appears first by ingestion route where as inhalation typically exhibits respiratory effects.

SYSTEMIC EFFECTS: Three clinical phases are seen:

1) Initial cholinergic phase

2) The intermediate syndrome (IMS)

3) Delayed polyneuropathy

1) THE CHOLINERGIC PHASE: [24, 27-32]

It is mainly because of accumulation of Ach at the cholinergic synapses and classified into

1. Muscarinic or hollow organ parasympathetic manifestations

2. Nicotinic or autonomic ganglionic and somatic (NMJ) effects and

3. Central nervous system (CNS) effects

CENTRAL NERVOUS SYSTEM MANIFESTATIONS:

Drowsiness, giddiness, tension, anxiety, restlessness, emotional liability, excessive dreaming, insomnia, headache, tremor, depression, confusion, slurred speech, generalized weakness, coma with absence of reflexes, type I paralysis, Cheyne Stokes respiration, convulsions, depression of respiratory and circulatory centers with dyspnea, cyanosis and hypotension.

TYPE I PARALYSIS described by Wadia, is indicative of acute neurotoxic effects during the cholinergic phase of poisoning. Patients present with giddiness, uneasiness, restlessness, anxiety and tremulousness followed by headache, ataxia, drowsiness, fasciculation, mental confusion and slurred speech.

The death is likely during this initial cholinergic phase because of its effects on the heart (bradycardia and other arrhythmias), respiratory failure (central or peripheral respiratory failure) and on brain (depression of vital centers). This cholinergic phase lasts for 24-48 hours.

2) THE INTERMEDIATE SYNDROME (IMS): [32-39]

Muscle paralysis occurs after recovery from cholinergic crisis, but before the expected, onset of the delayed polyneuropathy has been identified as “Intermediate syndrome” Wadia et al. in 1974 first described this type 2 respiratory paralysis and later christened as “Intermediate syndrome” by Senanayake, Karalliedde L. The syndrome is often acute in onset and seen within 24-96 hrs (1-4 days) after poisoning.

Muscular weakness involving proximal limb muscles and neck flexors are the cardinal features of this syndrome. The muscles innervated by motor cranial nerves III, VII and X are affected in different combinations. These patients are conscious and showed marked anxiety, sweating and restlessness caused by progressive hypoxia. The neck muscle weakness was a constant feature. Patients usually cannot raise their head above the pillows. Weakness of shoulder abduction and hip flexion was also noted. However normal strength in the distal muscles gives a false impression that the limbs are spared. Tendon reflexes are diminished or absent in most patients. There is no sensory impairment.

If adequate ventilator support is given then complete recovery occurs within 4-18 days. But altered function at neuromuscular junction may present up to 2yrs after its occurrence. The syndrome carries great mortality if not recognized in time and treated. Respiratory insufficiency develops over 6 hours approximately. Initially patient uses accessory muscles of ventilation. There is increase in respiratory rate, sweating, restlessness and later cyanosis. If not recognized soon patient becomes unconscious and death follows.

A consensus from literature search appears that IMS may result from inadequate therapy with oximes. IMS is likely due to post synaptic neuromuscular dysfunction. The symptom complex begins at a time when the cholinesterase function is very low and the OP compound is still detectable in the body. As blood levels of OPC's fall and OPC's tissue redistribution occurs the motor end plates may be re-challenged by the cholinesterase inhibitor in the presence of inadequate circulatory oximes.

3) DELAYED POLYNEUROPATHY: [29, 33, 40]

Though uncommon in India after cholinergic crisis the neuropathy develops following a latent period of 2-4 weeks. Distal muscular weakness of hand and feet are its main clinical features. The weakness is preceded by paresthesias of limbs and pain. Distal muscular wasting especially small muscles of the hand and those of anterior and peroneal compartments of the leg is an inevitable consequence. Pyramidal tract signs might appear after a few weeks or few months in some patients, recovery may differ. The Phosphorylation of an enzyme "neuropathy target esterase" in nervous tissue is considered to be responsible for the polyneuropathy.

OTHER EFFECTS OF POISONING:

- **Cardio vascular system:**[41-44]

Tachycardia and increased blood pressure occur in initial stage and bradycardia with decreased blood pressure in the late stage. Most common effect noticed was tachycardia but late onset bradycardia is attributed to direct action on myocardium by Organophosphorus compound. Hypertension occurs due to the combined effect of vasoconstriction from cholinergic stimulation of sympathetic ganglia and nor adrenaline release from adrenal medulla. Hypotension may also occur due to muscarinic action or blocking of ganglia by hyperpolarization. Cardiac manifestations including atrial fibrillation, conduction block and ventricular fibrillation and flutter usually occur in the terminal stage.

The cardiovascular actions of anticholinesterases are extremely complex as they reflect at any moment the algebraic sum of the excitatory and inhibitory actions of the

accumulated endogenous acetylcholine at several levels of the innervation of the heart and blood vessels i.e. at ganglionic, medullary, vasomotor and cardiac centers.

One of the major factors responsible for ECG changes is myocardial injury. ECG changes seen are sinus bradycardia, right axis deviation, AV block, ST segment depression in all leads and T wave inversion. A combination of metabolic and electrolyte derangements cause myocardial injury. Autonomic dysfunction and asynchronous repolarization produce variable QRS morphology and varying R-R interval. Sinus bradycardia could be due to effect of serum cholinesterase inhibition acting either directly on the myocardium and conducting tissues or through neurogenic mechanisms. Right axis deviation could be related to pulmonary edema. ST segment and T wave inversion has been suggested to be due to potassium shift or disturbance of other ions transport across membrane.

- **Respiratory system:**[45]

The most common terminal manifestation of OP poisoning is respiratory failure and it is produced by overstimulation of receptors at three levels.

1. Muscarinic action produces increased bronchial secretions, rhinorrhoea, bronchospasm and laryngospasm which can result in airway obstruction.
2. Nicotinic effects might cause respiratory muscles paralysis. Weakness of the muscles of the tongue and pharynx may lead to upper airway obstruction.
3. Depression of respiratory center may cause cessation of breathing. This is because of a direct action of the organophosphate at the cholinergic synapses in the brain stem that are responsible in the control of respiration.

Thomas Chang Yao Tsao et al. observed that the cardiovascular collapse was due to depression of the circulatory centre or due to profound hypoxemia, hypercapnia and acidemia from respiratory failure.

- **Gastro intestinal system:**[46,47]

After ingestion of Organophosphorus compounds, the initial symptoms are gastro intestinal of which increased salivation, nausea, vomiting, abdominal tightness, cramps and diarrhea are the common.

- **Effects on reproduction:**[47]

Abortions were reported in females due to OP poisoning.

- **Effects on temperature regulation:**[40]

It has been seen in many case studies with 7% as its incidence. Derangement of temperature regulation in the form of hypothermia. Some may develop fever which lasts for several days which is a biphasic response.

- **Vocal card paralysis:**[40]

Vocal cord paralysis within 2 days has been reported in few patients.

- **Eye:**

Miosis is a characteristic sign found in many patients with severe and moderately severe poisoning, but it is not invariably present. Mydriasis can also be seen. Fear, anger, pain and some other emotional stimuli are known to cause dilation of the pupil due to excessive stimulation of the sympathetic nervous system.

- **Joints:**

  Arthritis, cerebellar ataxia.

- **Interference with mitochondrial oxidative metabolism[40]**

Altered immunity to infection:

Severe cholinergic stimulation causes immune suppression either because of direct action of acetylcholine on the immune system or secondary to toxic chemical stress.

- **Behavioral effects:[48-50]**

Impaired memory and vigilance, reduced information processing and psychomotor speed, memory deficit, linguistic disturbances, depression, anxiety and irritability are the neuropsychological effects which were reported due to poisoning. After a period of 1 year who are free from poison exposure Duffy et al. Studied the brain electrical activity and noticed significant differences from the control group included increased beta activity, increased delta and theta slowing, decreased alpha activity and increased amounts of rapid eye movement (REM) sleep. Perfusion defects especially in the parietal lobe have been detected on brain single photon emission computerized tomography (SPECT) after OP poisoning.

- **Extra pyramidal manifestation:[51, 52]**

These might occur after 4 – 40 days of OP poisoning. In those who survive the symptoms might disappear within 1-4 weeks. The features include dystonia, resting tremor, cog-wheel rigidity and choreoathetosis and these are usually bilateral and in some

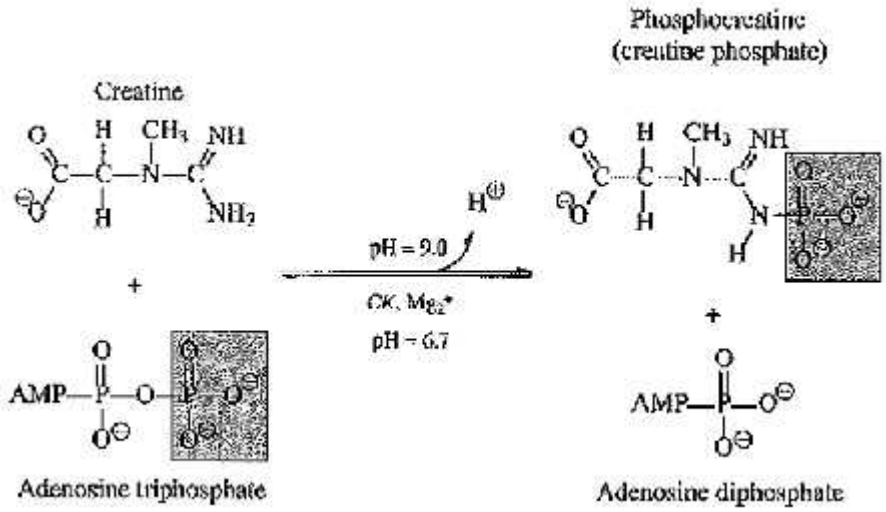
cases it may be asymmetrical. This phenomenon has been attributed to the inhibition of acetyl cholinesterase in the human extra pyramidal system which is rich in cholinergic neurons and anticholinesterase. Recent studies suggest that Parkinson's disease is more common in patients who report previous exposure to pesticides. Glutathione transferase polymorphisms may influence the body's ability to detoxify pesticides and may increase patient's susceptibility to Parkinson's disease after pesticide exposure.

PATHOPHYSIOLOGY OF SERUM CPK: [53]

Creatine kinase (EC 2.7.3.2; adenosine triphosphate, creatine N-phosphotransferase CK) is a dimeric enzyme that catalyzes the reversible Phosphorylation of creatine by adenosine triphosphate (ATP).

Physiologically, when muscle contracts ATP is converted to ADP (adenosine diphosphate) and CK catalyzes the rephosphorylation of ADP to ATP using creatine phosphate as the Phosphorylation reservoir.

FIGURE 1: FORMATION OF CREATINE PHOSPHOKINASE



Many metal ions inhibit the enzyme. Excess ADP, citrate, fluoride, nitrate, acetate and thyroxin also inhibits the enzyme activity in serum.

CK activity is greatest in striated muscles and heart tissues which contain some 2500 and 550 U/g of proteins respectively. Other tissues such as brain, GI tract, urinary bladder contain significantly lesser amounts.

CK is a dimer composed of 2 subunits each with molecular weight of 40,000 Da. These subunits (B & M) are the products of loci on chromosome 14 and 19 respectively. Because the active form is a dimer only 3 forms of subunits can exist – BB (CK-1), MB (CK-2) and MM (CK-3). All these 3 isoenzymes are present in the cytosol of the cell. However a 4th form CK-Mt is located between the inner and outer membranes of the mitochondria and constitutes in heart up to 15% of total CK activity.

TABLE 4: CK ISOENZYMES DISTRIBUTION

Isoenzyme name	Composition	Present in	Elevated in
CK-1	BB	Brain	CNS diseases brain tumors
CK-2	MB	Heart	Acute myocardial infarction
CK-3	MM	Skeletal muscle	Skeletal muscle diseases

Clinical significance:

Serum CK is increased in nearly all patients when injury, inflammation or necrosis of skeletal or heart muscle occurs.

Elevation of CK may be the only sign of subclinical neuromuscular disorder. Serum CK activity is greatly elevated in all types of muscular dystrophy (particularly Duchene).

High values of CK are noted in viral myositis, polymyositis and similar muscular diseases.

However, in neurogenic muscle diseases such as myasthenia gravis, multiple sclerosis, poliomyelitis and Parkinson's, serum CK is not increased.

Skeletal muscle that is diseased or damaged may contain CK-MB leading to increase in serum CK-MB isoenzymes and also sometimes in chronic kidney disease (uremic myopathy).

In acute rhabdomyolysis due to crush injury, with severe muscle destruction, serum CK activities exceeding 200 times the upper limit may be found. If the CK remains below 5000 U/L (about 30 times the upper limit) during the first 3 days after the insult, the probability of developing renal failure appears to be low.

Serum CK can also be increased by other direct trauma to muscle including intramuscular injections and surgical intervention.

Various drugs such as statins, fibrates, antiretroviral drugs and ARB's can increase serum CK activity.

Reference intervals – Serum CK is subject to a number of physiological variations. In males, the reference interval is 46 – 171 U/L and in females, it is 34 – 145 U/L.

GRADING OF SEVERITY OF ORGANOPHOSPHORUS POISONING:

MODIFIED DREISBACH CLINICAL CRITERIA[115]

GRADE I - Mild symptoms related to portal of entry

Nausea, vomiting in case of ingestion

Cough, burning sensation in the chest in case of inhalation

Mild systemic symptoms like headache, dizziness, weakness

GRADE II - Moderate systemic poisoning

Abdominal pain, diarrhea in case of ingestion

Tightness in chest, difficulty in breathing in case of inhalation

Salivation, lacrimation, sweating, pupillary changes

Bradycardia, confusion, tremor, restlessness

GRADE III - Severe systemic poisoning

Respiratory depression, generalized weakness

Cyanosis, peripheral circulatory failure, convulsions and coma

FACTORS INFLUENCING ORGANOPHOSPHORUS COMPOUND TOXICITY:

1. Dose - Lethal effects due to the severe cholinergic effects are due to the inhibition of acetylcholinesterase enzyme. Larger the dose more severe the manifestations.
2. Age and sex - Young children have low levels of metabolizing enzymes, so increased mortality. Lethal dose for males is greater than that in females.
3. Malnutrition-Due to decreased activity of enzymes, the lethal dose needed is less.
4. Effect of impurities and storage - Impurities in pesticide may be of low toxicity or more toxic than the major component or they may be potentiators of toxicity of other compounds. Toxicity of some Organophosphorus compounds increase when they are stored in tinned steel containers.
5. Effect of other pesticides — Exposure to more than one pesticide will have an additive effect. One Organophosphorus compound may influence the toxicity of other compound by interfering with metabolic activation and disposal.
6. Species - Birds are more sensitive to Organophosphorus compounds. Amphibians are less sensitive than mammal.

DIAGNOSIS AND MANAGEMENT OF ORGANOPHOSPHORUS POISONING

DIAGNOSIS OF ORGANOPHOSPHORUS POISONING:

Diagnosis of OPC poisoning is mainly depends on its clinical features, and history of exposure to a known OP compound. Estimation of serum or RBC cholinesterase level and electro diagnostic test confirms the diagnosis. For the appearance of clinical features in OP poisoning the RBC cholinesterase activity should be <75% of normal and <10% in clinically overt poisoning patients. In general, however, serial studies have failed to document a strict relationship between the severity of clinical manifestations and prognosis.

LABORATORY INVESTIGATION

Diagnosis of cholinergic excess is mainly clinical and requires quick recognition of the syndrome and a highly observant clinical setting.

1) Serum and Red Blood cell ChE activity - To confirm the exposure to an OP compound and to monitor prognosis of the patient. A 50% reduction in the activity of the enzyme is considered confirmatory for OP poisoning. An incremental response in enzyme activity is seen with treatment.

2) Serum electrolytes, creatinine and urea- To assess the rate of volume depletion in the presence of muscarinic secretory loses from the pulmonary and alimentary tracts.

3) Blood Urea Nitrogen (BUN) Monitoring.[15]- To predict the development of relapse in OP poisoning. Elevation from its normal range [8-20 mg/dl] is seen in acute poisoning

4) Arterial Blood Gas (ABG) analysis[16]-To assess the rate of hypoxia and/or hypercapnia in the presence of respiratory distress from pulmonary congestion.[15]

5) Hyperglycemia (serum glucose) – It has been reported in many studies. The increase in serum glucose is due to secondary release of catecholamine from the adrenal medulla.[14]

6) Serum Amylase – Many case reports have shown a rise in serum Amylase level following ingestion of Organophosphorus poison with or without the development of Pancreatitis.[17]

7) Leukocyte Number – Leucocytosis is a common finding in OP intoxication. It helps to assess the prognosis and efficiency of treatment.

8) Imaging Studies

- Chest X-ray for evaluation of pulmonary edema (or) congestion.
- CT/USG Abdomen to evaluate the pancreatic status.[17]
- In patients with altered mental status CT scan of the head can be considered.

Other Tests

Electrocardiogram (ECG)

Helps in ruling out rare dysrhythmias such as ventricular tachycardia, atrial fibrillation and torsades de pointes (or) QT prolongation.

MANAGEMENT OF ACUTE ORGANOPHOSPHORUS POISONING: [27, 54, 58-61]

1. First Aid and supportive measures:

- Remove patient from the contaminated environment.
- Remove contaminated clothing
- Wash skin with soap and water and eyes with water
- Assess breathing and circulation
- Resuscitate if necessary
- Support vital functions if necessary
    - O2 inhalation
    - Lung ventilation
    - Inotropes
    - Control of convulsions
    - Monitor ECG, blood pressure, blood sugar, O2 saturation, ventilation, level of consciousness.

2. **Prevention of absorption:**

- Decontamination
- Emesis
- Adsorbent
- Cathartics
- Bowel wash

3. Specific chemotherapy:

- Atropine
- Oximes

4. Treatment of complications

I. **Supportive measures:**

ABC - maintenance of airway, breathing and circulation.

Definitive airway protection (endotracheal intubation) is required in unconscious patients to minimize the risk of aspiration and to facilitate the respiratory care if there is deterioration.

II. **Prevention of absorption:**

a. Decontamination: Gastric lavage (performed within one hour of poison consumption) is effective. Activated charcoal (1mg/kg) is useful though currently there is no evidence that either single dose or multiple dose regimens results in clinical benefit.

b. Emesis: Unless the patient is comatose, convulsing or lost the gag reflex, emesis should be initiated. If these contraindications are present, endotracheal intubation should precede gastric lavage with wide bore tube.

c. Adsorbent: Activated charcoal functions as an adsorbent and should be given within 3 hours of ingestion and if gastric emptying is delayed it may be useful for up to 12 hours after ingestion. It is the most valuable single agent for emergency management of oral drug poisoning.

d. Cathartics: Cathartics function by decreasing absorption and increasing elimination. It should be administered as early as possible because relapse is thought to be due to delayed absorption.

e. Bowel wash: To be done twice a day, helps to remove toxic substances from large bowel.

III. **Specific chemotherapy**

REVERSAL OF SYNAPTIC BIOCHEMICAL ABNORMALITIES AND REVERSAL OF CHOLINESTERASE BLOCKADE - with atropine, glycopyrrolate and oximes.

Atropine - It is an alkaloid derived from a plant Atropabelladona and Daturastramonium. It is the physiological antidote for acetylcholine and blocks it at muscarinic and not at nicotinic receptors. The onset of action is within 1-4 minutes and peak effect is in 8 minutes.

Out of the various signs of atropinization the target endpoints for atropine therapy are

Targeted End – Points of Atropinization

- Clear lungs
- Dry axillae
- Systolic BP > 80mm Hg
- Heart rate > 80 /min
- No Miosis

Dose – Given as 1-2 mg IV and the dose is doubled every 5-10 minutes when there is no effect. In massive exposure, large doses (300-1500mgs/day) of atropine may be needed by continuous IV infusion.

The patient should be reviewed and assessed every 15 minutes to see the adequacy of dosage. If clinical features recur, further increment in boluses and infusion (doubling) is required. Once the parameters have settled, the patient is seen at least hourly for the next 6 hours to check the effectiveness of atropine infusion. Studies have found that continuous atropine infusion is more effective than intermittent boluses in decreasing respiratory failure and mortality.[62, 63] As the required dose of atropine falls, observation for recurrence of cholinergic features can be done less often (every 2-3hrs). Atropine is partially detoxified in the liver and partly excreted unchanged by the kidney.

TABLE NO. 5- ATROPINE RECOMMENDATIONS IN MAJOR TEXT BOOKS OF

INTERNAL MEDICINES AND NATIONAL FORMULARIES.[20]

Source	**Recommended Regimen to achieve Atropinization**	**Marker of Atropinization**
Australian Medicines hand book 14th Edition, 2003	2 mg IV repeated until Atropinization is achieved then infusion titrated against clinical effects.	Abolish all secretions
British National Formulary Edition - 46, 2003	2 mg repeated every 5 – 10 min. IM (or) I.V according to severity	Dry Flushed skin, Dilated pupils, tachycardia
Harrison's Internal Medicine Edition – 18th, 2011	0.5 – 2mg repeated every 5-15 min	Dry secretions.
WHO model formulary Edition - 1, 2002	2 mg repeated every 20-30 min	Flushed early skin and tachycardia

The markers used to detect atropine toxicity are – confusion, pyrexia, absent bowel sounds and urinary retention. Respiratory failure is being the most common cause and mortality in the early period of poisoning (usually <48 hours) is inadequate atropinization.

Glycopyrrolate - (Dose - 0.05mg/kg) The main advantages of glycopyrrolate over atropine are - nil central toxicity (central anti cholinergic syndrome) as it is a quaternary ammonium compound and hence has no CNS penetration, lesser tachycardia, and better control of tracheobronchial secretions resulting in lower incidence of respiratory tract infection.

Oximes- Amongst the various oximes like obidoxime, diacetylmonoxime, and bisaldoxime, pralidoxime (2-PAM or P2AM–2 hydroxy iminomethyl-1-methyl pyridinium chloride) is most often used worldwide. They prevent continued toxicity by scavenging (direct reaction and detoxification) the remaining Organophosphorus (OP) molecule. They also have an endogenous anticholinergic effect in normal doses. Their major effects are on the peripheral nervous system (PNS) where they reverse the cholinergic nicotinic effects like muscle weakness and fasciculation and hence aid in recovery of neuromuscular transmission. It prevents the development of IMS when started early and also helps in rapid recovery in patients on ventilator due to IMS. Since its lipid solubility is low and has limited CNS penetration and activity.

The therapeutic effectiveness (window) of oximes depends upon

- Concentration of poison consumed (poison load)
- Time elapsing between poisoning and oxime administration

- Type of the OPC consumed oximes has greater effect on diethyl compounds (parathion, diazinon) than dimethyl compounds (malathion, methyl dematin). This is due to the fact that diethyl compounds reactivate and age at significantly slower rate than dimethyl compounds
- Concentration of oximes in the blood
- Release of OPC from lipid stores over a prolonged time

OPC is not a single entity with sublential variability in clinical course, response to oximes and outcome[62]

1-3 gms/day is the usual dose of P2AM in India and after 48 hours it is said to have no role.[64-67]

For effective treatment of OP toxicity the Serum levels of P2AM should be > 4mg/lit.[66, 67] To achieve these serum levels and as the elimination T1/2 of P2AM is 1.2 hrs, it is given in a bolus dose of 20-40mg/kg followed by 500mg/hr as a continuous infusion. **30mg/kg followed by an infusion of >8mg/kg/hr is the loading dose which is recommended by WHO.[64]** The therapeutic endpoint for P2AM therapy is the resolution of muscle fasciculation and weakness, reactivation and permanent clinical improvement and increase in SChE levels.[68] After stopping of the P2AM the improvement in SChE should be seen for at least three days. The present recommendation is that P2AM should be started early with higher doses being given for several days till recovery. The duration of treatment is to be monitored by SChE levels. **In carbamates the P2AM is not effective but are not contraindicated in therapy.** However, clinical experience in the developing world has led to doubt about the clinical relevance of oximes for any form of

OPC poisoning.[64] In a recent randomized trial, Pawar et al[69] reported that hyper dose of pralidoxime than the standard WHO recommended dose underlying a 2 gm loading dose followed by 1 g/hour, pralidoxime was very beneficial with very low mortality.

A prospective non randomized study done by Shivakumar S et al[70] has revealed that high dose pralidoxime with ventilator support and adequate atropine reduces mortality.

OTHER THERAPIES:

1. Clonidine: The release of acetylcholine from central and peripheral cholinergic neurons which is inhibited by clonidine. Clonidine pretreatment (0.3 mg/kg) increased the onset latency to tremor from 5 to 20 min, increased the onset latency to death from 12 to 24 min and increased the percentage of survivors to 50% following poisoning with physostigmine. Protective effects of clonidine are reversed by Yohimbine (1mg/kg). It was suggested that central cholinergic neurons involved in the regulation of respiration and fine motor control, but not peripheral motor neurons, are inhibited by the action of clonidine on α receptors.[72, 73]
2. The addition of benzodiazapines to atropine and P2AM decreases cardiac and brain morphological damage from OPP induced seizures.[74]
3. Use of phenytoin is not recommended due to its membrane stabilizing and autonomic effects.[67]
4. Magnesium sulphate blocks Ligand gated calcium channel, resulting in decreased acetylcholine release from pre-synaptic terminals, thus improving function at

neuromuscular junctions, and decreased CNS over-stimulation mediated via NMDA receptor activation.

5. Sodium bicarbonate is sometimes used for treatment of OP poisoning in place of oximes. Increases in blood pH (up to 7.45 – 7.55) have been reported to improve outcome in dogs through an unknown mechanism.[75]
6. FFP- the administration of plasma (fresh frozen or freshly prepared) may prevent the development of IMS and related mortality. In patients with OPP, it increases the SChE levels and it may be used as an alternative or adjunctive treatment method especially in patients not receiving P2AM. However further randomized and animal studies are required to infer a definitive result.[76]

DRUGS FOR FUTURE:

HuperzineA:

HupA has been proved to be strong, very specific and reversal inhibitor of AChE. In 1996 by an author named Zhu developed a new drug Shuangyiping, which is a tablet form of HupA developed from extracts of Huperziaserrata for symptomatic treatment of Alzheimer's disease (AD) in China. HupA is also marketed in the USA as a dietary supplement (as powdered Huperziaserrata in tablet or capsule form). Phase IV clinical trials in China have demonstrated that HupA significantly improves memory deficits in elderly people with benign senescent forgetfulness and in patients with AD or vascular dementia (VD), with minimal peripheral cholinergic side effects and no unexpected toxicity. HupA has better penetration through the blood–brain barrier, higher oral bioavailability and longer duration of AChE inhibitory action .[77]

Butane - 2, 3-dionethiosemicarbazone is an oxime with antioxidant properties. It has been demonstrated that butane - 2,3-dionethiosemicarbazone has an antioxidant activity in scavenging different forms of reactive species (which are commonly generated in normal cellular oxygen metabolism playing some biological roles) like hydroxyl radicals, nitric oxide radicals, and hydrogen peroxide and as well as counteract its formation. It is also able to effectively counteract the lipid peroxidation induced by different oxidant agents. In ex vivo experiments it has been observed that the oxime depicted no significant change in glutathione levels. An in vitro study examined the capacity of this oxime to scavenge different forms of reactive species.[78]

IV. **TREATMENT OF COMPLICATIONS**:

Seizures, Pulmonary edema, Pneumonia, Adult respiratory distress syndrome (ARDS), renal failure, Hypotension / shock, arrhythmias, etc. are all managed as per standard protocol.[79]

MATERIALS AND METHODS

SUBJECTS: Patients presenting with Organophosphorus poisoning were the study subjects.

STUDY DESIGN: A prospective study.

ETHICAL COMMITTEE APPROVAL: The Ethical committee approval was obtained to carry out the study in the hospital.

STUDY SETTING:

STUDY DURATION: NOV 2015- JUNE 2017

MATERIALS:

A total of 662 patients with poisoning were admitted to the hospital during the study period and among them 295 cases were Organophosphorus compound detected and 80 patients were included in the study after applying inclusion and exclusion criteria.

STUDY CRITERIA:

INCLUSION CRITERIA:

All patients with a history of consumption and/or exposure of OP poison of either sex admitted to hospital within 12 hours of ingestion and not having been treated outside.

EXCLUSION CRITERIA:

Patients with indication of exposure to a entirely different poison other than OP poison.

- Patients with OP poisoning and mixed with any other poison
- Patients who have consumed poison along with alcohol
- Patients who are chronic alcoholics
- Patients with history suggestive of chronic liver disease
- History suggestive of myopathy
- Patients with history of malignancy and autoimmune diseases
- Patients with history of renal disease
- History of intake of drugs like – Eg: Statin, Fibrate, Dexamethasone

STUDY PROTOCOL:

Patients admitted in _____ _____ were the study group. Information was collected through a preformed and pre-tested proforma from each patient. Qualifying patients were subjected for detailed history, clinical examination and biochemical examinations. Admissions were always through the emergency department where initial decontamination procedures were carried out. A detailed clinical examination was carried out with particular reference to vital parameters, pupil size, assessment of all the others systems as per prescribed proforma. This examination took place during initial presentation and the cases were followed up during treatment of the patients. Modified Dreisbach clinical criteria was applied to all the study subjects and the severity of OP poisoning was graded as mild, moderate, severe at the time of admission.

In all the study subjects, 3ml of blood was drawn on admission before administration of atropine, plasma cholinesterase and serum creatine phosphokinase were estimated, apart from serum CPK and serum cholinesterase other relevant and routine investigations were done as per need.

OBSERVATION AND RESULTS

This study was done at _____ _____ from November 2015 to June 2017. A total of 80 cases of Organophosphorus poisoning were studied.

Table 6: Distribution of cases according to Age

Age Groups (Yrs)	**N**	**%**
≤20	19	23.8
21-30	31	38.8
31-40	16	20
41-50	11	13.8
>50	3	3.8
Total	80	100

Descriptive Statistics	**Minimum**	**Maximum**	**Mean**	**SD**
Age (Yrs)	15	58	29.5	10.9

Majority of the patients were in the age group of 21-30 years which comprised 38.8% of the study population. 23.8% of patients were in the age group of <20 years, 20% of patients in the group 31-40 years, 13.8% of patients in the group 41-50 years and 3.8% of patients were above 50 years of age and minimum age group is 15 years and maximum age is 58 years respectively.

Figure 2: Distribution of cases according to Age

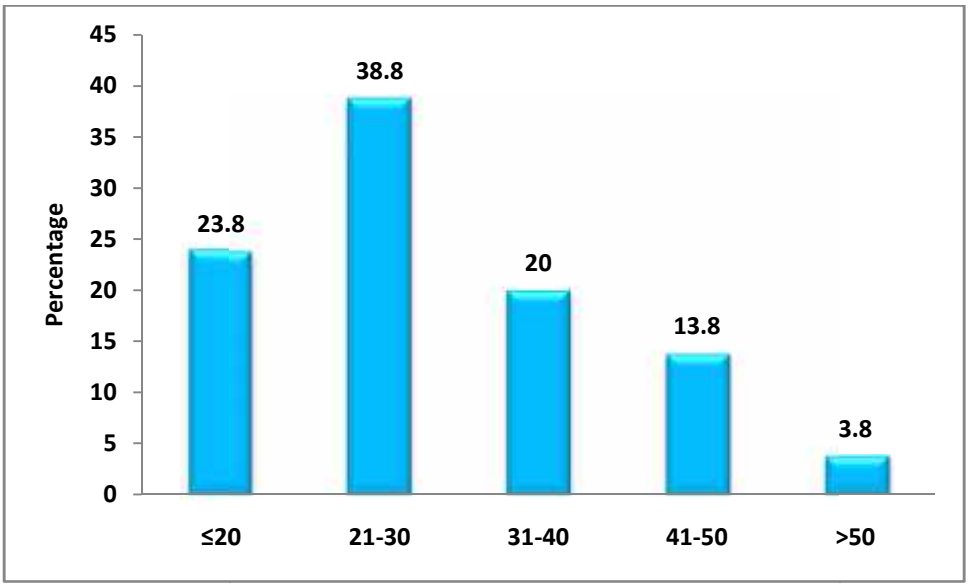


Table 7: Distribution of cases according to Sex

Sex	N	%
Male	39	48.8
Female	41	51.3
Total	80	100

M/F ratio	0.95

In our study 51.3 % were females and 48.8% were males with M/F ratio 0.95 respectively.

Figure 3: Distribution of cases according to Sex

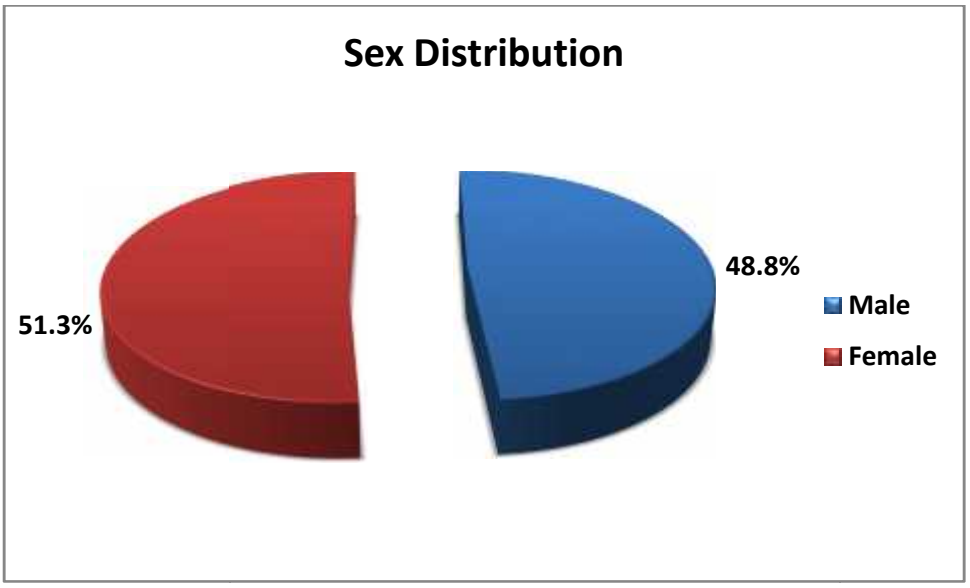


Table 8: Distribution of cases according to Occupation

Occupation	N	%
Farmer	28	35
Govt Job	4	5
House Wife	21	28.8
Private Job	4	5
Self Employed	6	7.5
Student	15	18.8
Total	80	100

35% (28 cases) of the OP poisoning cases were seen in agriculturists and 28.8% (21 cases) were housewife and among students 18.8% (15 cases).

Figure 4: Distribution of cases according to Occupation

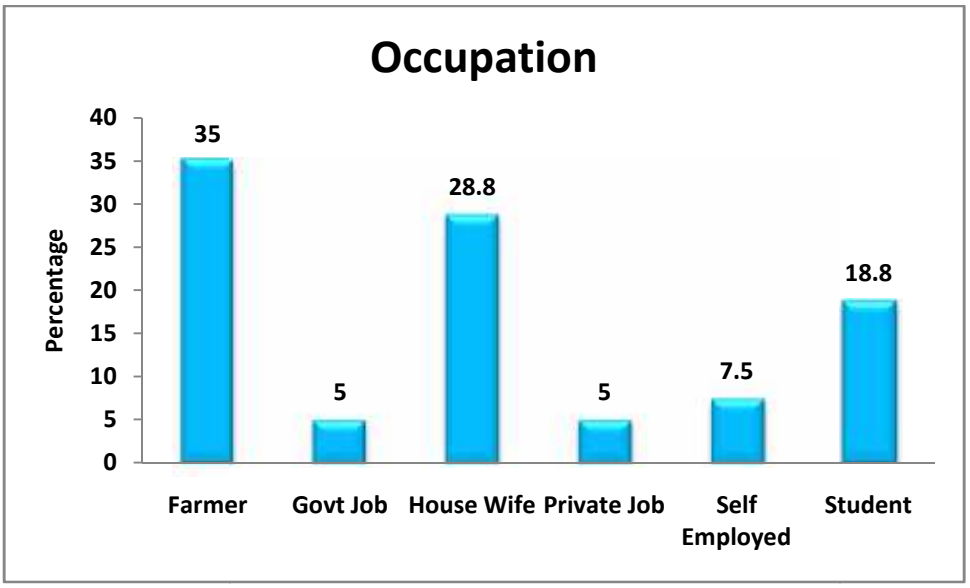


Table 9: Distribution of cases according to Education

Education	N	%
Illiterate	51	63.8
Primary School	9	11.3
High School	9	11.3
PUC	5	6.3
Degree	6	7.5
Total	80	100

Out of 80 patients under study, majorities were illiterates, 51 patients (63.8%), followed by patients educated till primary and high school level were 9 patients (11.3%) respectively and 6 cases (7.5%) in degree holders, and 5 patients (6.3%) completed their education till PUC.

Figure 5: Distribution of cases according to Education

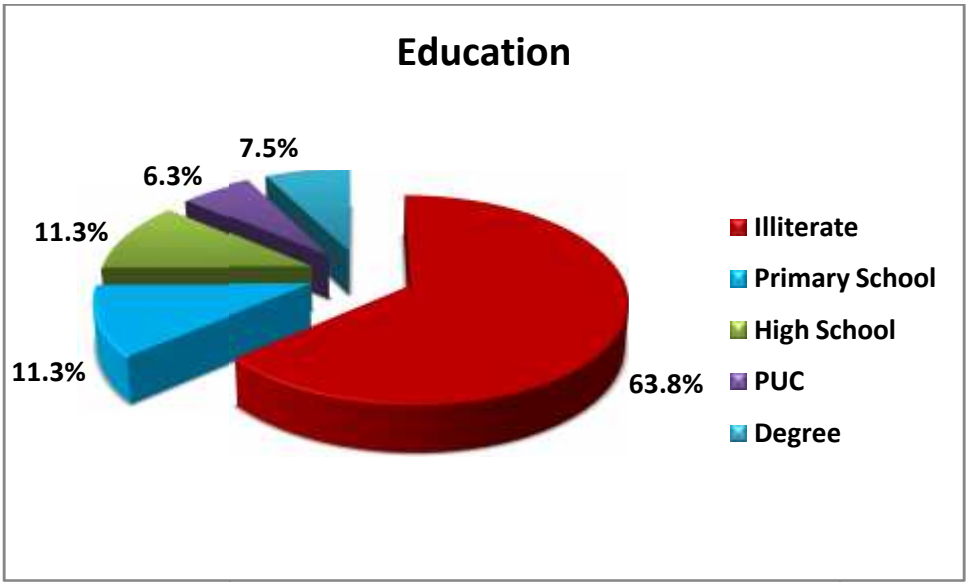


Table 10: Distribution of cases according to Route of Exposure

Route of Exposure	N	%
Skin contact	1	1.3
Inhalational	0	0
Oral	79	98.8
Total	80	100

In our study, 79 out of 80 cases had oral ingestion as the major route of poisoning and only 1 had accidental exposure to skin contact with Dichlorovas.

Figure 6: Distribution of cases according to Route of Exposure

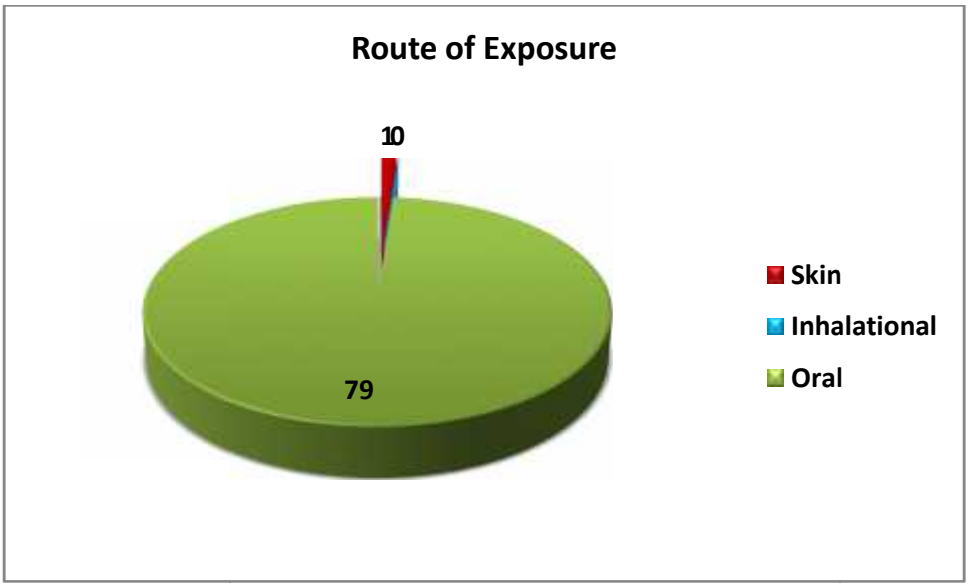


Table 11: Distribution of cases according to Regional distribution

Regional distribution	N	%
Rural	49	61.3
Urban	31	38.8
Total	80	100

In our study, 49 out of 80 cases which accounted for 61.3%, were from rural area and 31 cases (38.8%) were from urban area.

Figure 7: Distribution of cases according to Regional distribution

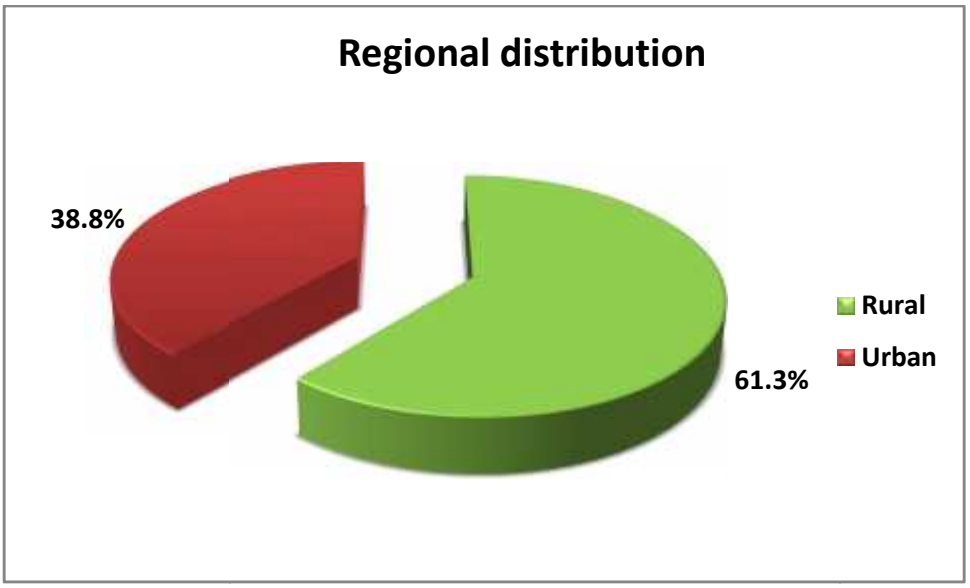


Table 12: Distribution of cases according to Reason for exposure to OP Poison

Reason	N	%
Accidental (Skin)	1	1.3
Intentional	79	98.8
Total	80	100

In our study main reason for majority of poison consumption was intentional which accounted for 98.8% 79 patients and only 1 patient had accidental exposure on skin with Dichlorovas.

Figure 8: Distribution of cases according to Reason for exposure to OP Poison

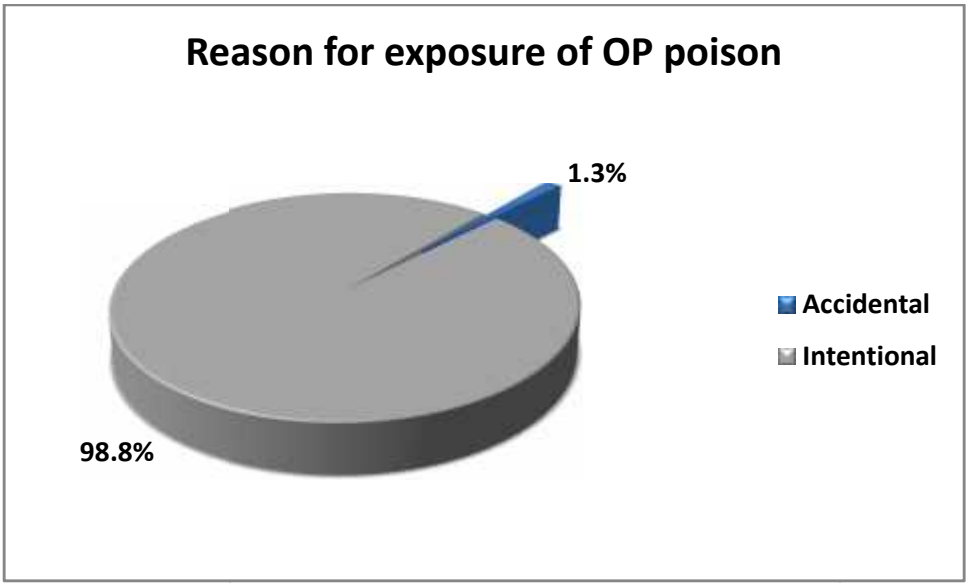


Table 13: Distribution of cases according to OP Compound

Compound	N	%
Chlorpyriphos	2	2.5
Dichlorvas	18	22.5
Dimethoate	6	7.5
Malathion	22	27.5
Methylparathion	3	3.75
Monocrotphos	21	26.25
Phorate	1	1.25
Triazophos	2	2.5
Phenylphyrazole	1	1.25
Prophenofus+Cypermethrin	2	2.5
Phosphonic acid	1	1.25
Methacriphos	1	1.25
Total	80	100

Out of 80 patients under study, 22 patients (27.5%) were consumed malathion followed by monocrotphos 21 patients (26.25%) and 18 patients (22.5%) were consumed dichlorvas.

Figure 9: Distribution of cases according to OP Compound

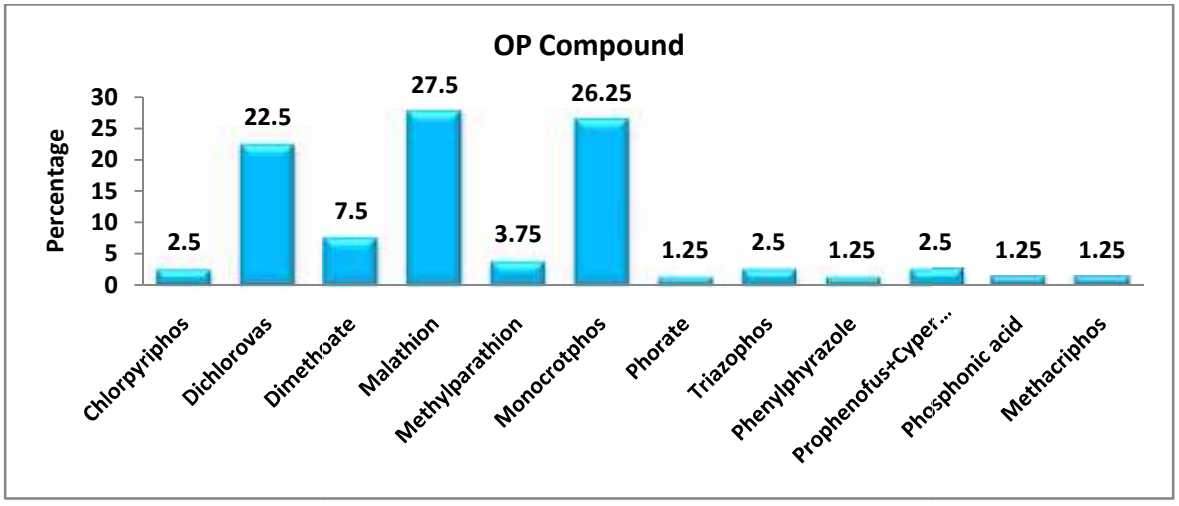


Table 14: Distribution of cases according to OP Detected by TLC Method

	N
Total poisoning	662
OP Detected	295
Study Sample	80

A total of 662 patients with poisoning were admitted to the hospital during the study period and among them 295 cases were Organophosphorus compound detected by TLC (thin layer chromatography) method and 80 patients were included in the study, after applying inclusion and exclusion criteria.

Figure 10: Distribution of cases according to OP Detected OP Detected by TLC Method

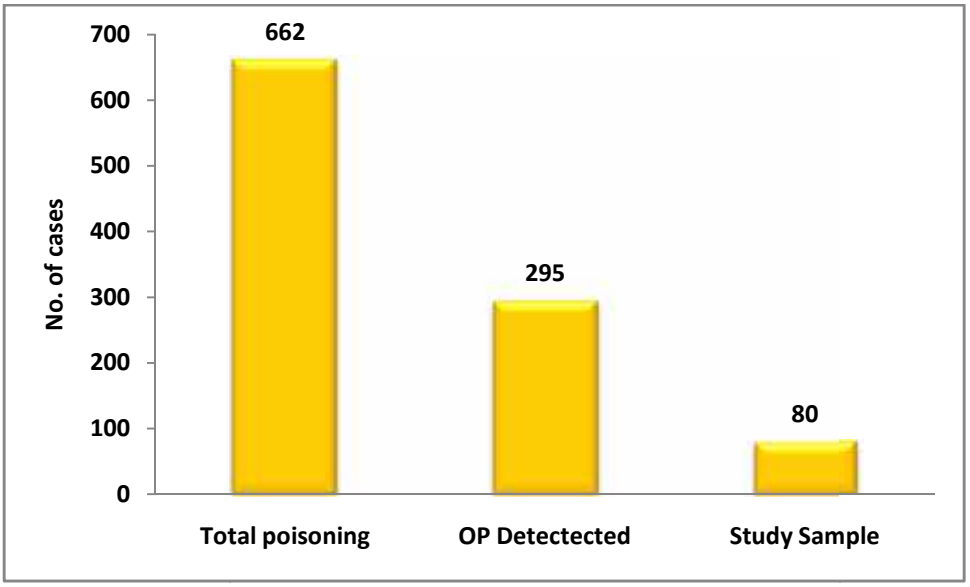


Table 15: Distribution of cases according to clinical outcome

Clinical outcome	N	%
Survived without ventilatory support	72	90
Survived with ventilatory support	6	7.5
Death with ventilatory support	2	2.5
Total	80	100

Out of 80 patients under study, 72 patients which accounts for 90% have survived without ventilatory support and 6 patients 7.5% have survived with ventilatory support and 2 cases 2.5% of patients died with ventilatory support.

Figure 11: Distribution of cases according to clinical outcome

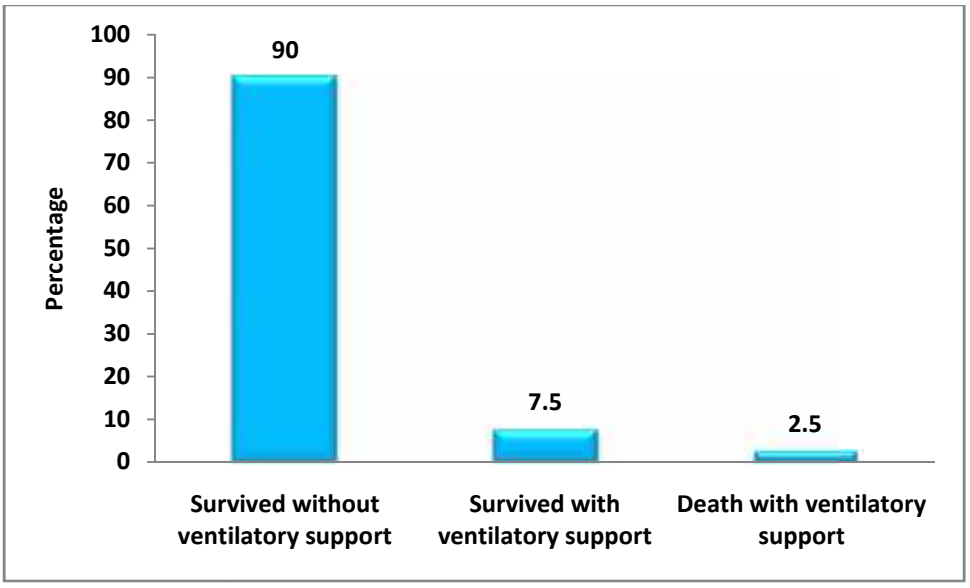


Table 16: Distribution of cases according to Dreisbach'S Classification

Dreisbach'S Classification	N	%
Mild	48	60
Moderate	25	31.3
Severe	7	8.8
Total	80	100

Out of 80 patients under study, 48 patients out of 80 cases (60%) were in clinical severity grade 1 and 25 patients (31.3%) in clinical severity grade 2 and 7 patients (8.8%) in clinical severity grade 3 respectively.

Figure 12: Distribution of cases according to Dreisbach'S Classification

Table 17: Association of Dreisbach'S Classification and Age

Age groups	Total no of cases	Dreisbach'S classification						p value
		Mild		Moderate		Severe		
		N	%	N	%	N	%	
≤20	19	11	57.9	6	31.6	2	10.5	0.647
21-30	31	19	61.3	11	35.5	1	3.2	
31-40	16	8	50.0	6	37.5	2	12.5	
41-50	11	8	72.7	2	18.2	1	9.1	
>50	3	2	66.7	0	0.0	1	33.3	
Total	80	48	60.0	25	31.3	7	8.8	

Most common age group in our study is 21-30 years, 19 patients had mild poisoning, 11 patients had moderate poisoning. In the age group 11-20 years, 11 patients had mild poisoning and 6 had moderate poisoning. Severe poisoning was observed in 2 patients each in 11-20 years and 31-40 years and one each in all other age groups.

Figure 13: Association of Dreisbach'S Classification and Age

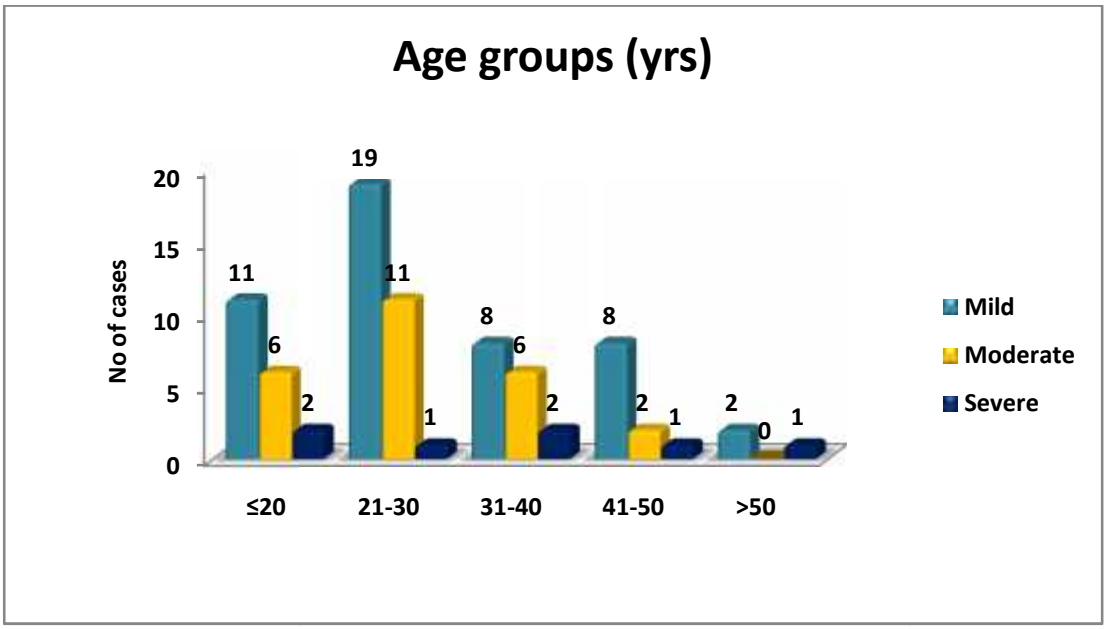


Table 18: Association of Dreisbach'S Classification and Sex

Sex	Total no of cases	Dreisbach's classification						p value
		Mild		Moderate		Severe		
		N	%	N	%	N	%	
Male	39	26	66.7	10	25.6	3	7.7	0.49
Female	41	22	53.7	15	36.6	4	9.8	
Total	80	48	60.0	25	31.3	7	8.8	

In our study, 26 out of 39 patients were male and 22 out of 41 patients were females had mild poisoning, 15 out of 41patients were females and 10 out of 39 patients were males had moderate poisoning. Severe poisoning is seen in 4 out of 41 patients in females and 3 out of 39 patients in males respectively.

Figure 14: Association of Dreisbach'S Classification and Sex

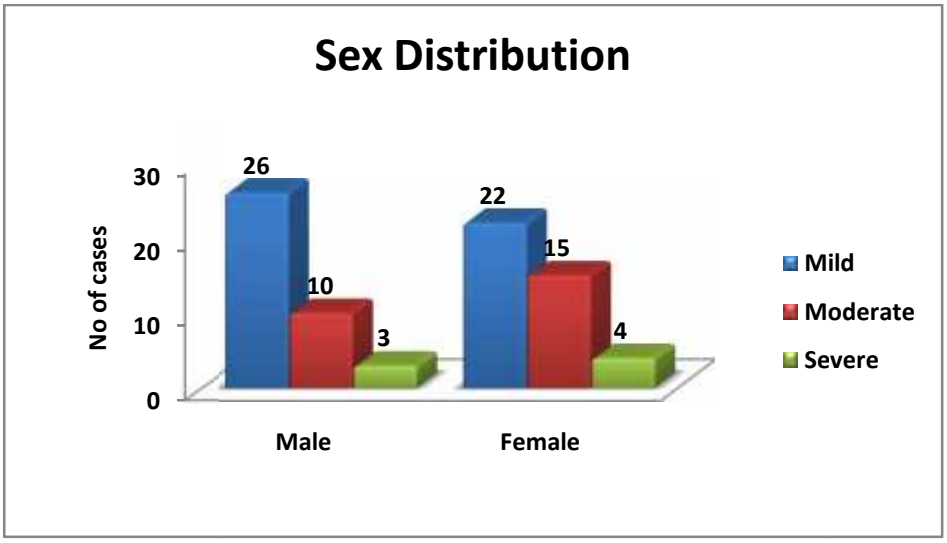


Table 19: Association of Dreisbach'S Classification and Lost to follow-up

Lost to Follow Up	Total no of cases	Dreisbach's classification						p value
		Mild		Moderate		Severe		
		N	%	N	%	N	%	
	1	0	0.0	1	100.0	0	0.0	-
Total	80	48	60.0	25	31.3	7	8.8	

48 patients out of 80 patients had mild poisoning, 25 patients had moderate poisoning, and severe poisoning is seen in 7 patients. 2 patients in moderate poisoning had lost follow up because the patient went against medical advice and among them 1was on mechanical ventilation.

Figure 15: Association of Dreisbach'S Classification and Lost to follow-up

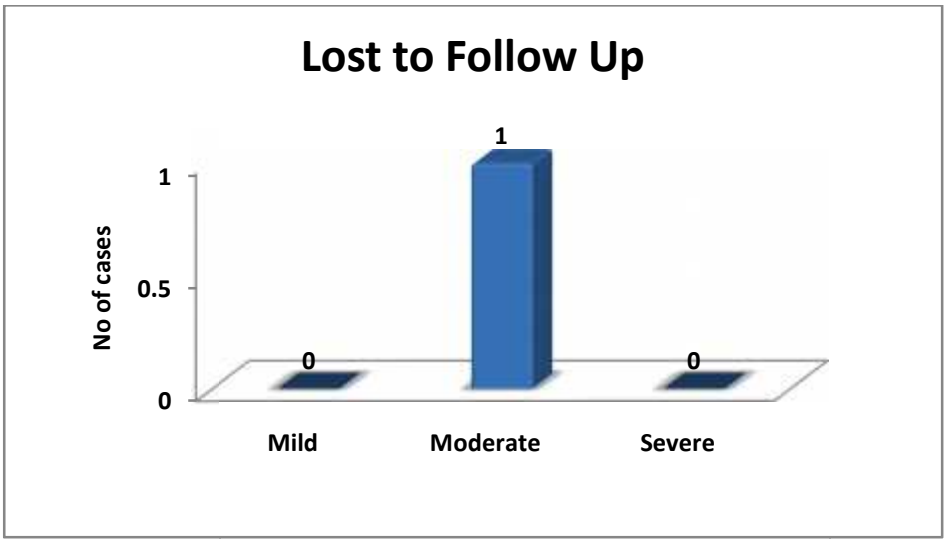


Table 20: Association of Dreisbach'S Classification and OP poisoning

OP Detected	Total no of cases	Dreisbach's classification						p value
		Mild		Moderate		Severe		
		N	%	N	%	N	%	
Yes	80	48	60.0	25	31.3	7	8.8	-
Total	80	48	60.0	25	31.3	7	8.8	

A total of 295 cases of OP compound detected patients, 80 were cases were included in study group of which 48 out of 80 cases had mild poisoning, 25 out of 80 cases had moderate poisoning and 7 out of 80 cases had severe poisoning.

Figure 16: Association of Dreisbach'S Classification and OP poisoning

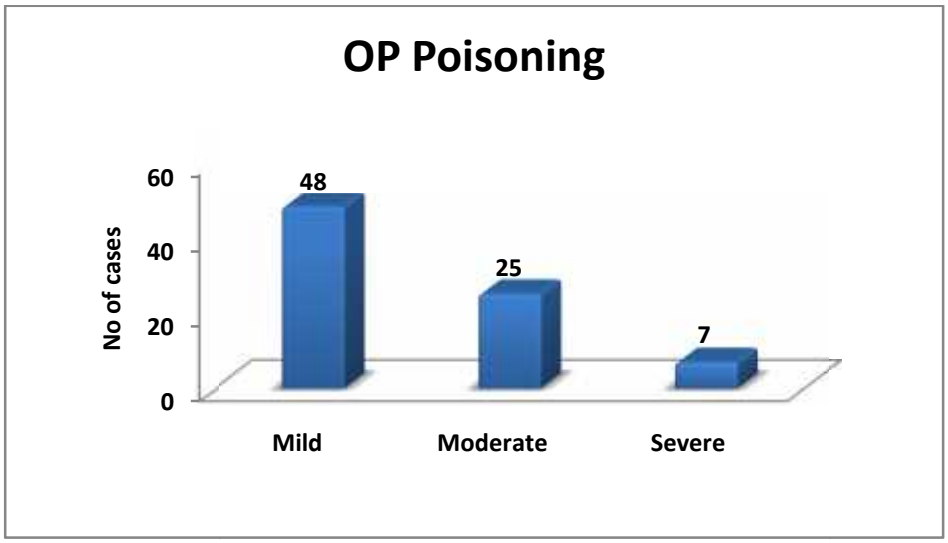


Table 21: Association of Dreisbach'S Classification and clinical outcome

Clinical outcome	Total no of cases	Dreisbach's classification						p value
		Mild		Moderate		Severe		
		N	%	N	%	N	%	
Survived without ventilatory support	72	48	66.7	21	29.2	3	4.2	0.263
Survived with ventilatory support	6	0	0.0	4	66.7	2	33.3	0.013*
Death with ventilatory support	2	0	0.0	0	0.0	2	100.0	0.62
Total	80	48	60.0	25	31.3	7	8.8	

Note: *means significant at 5% level of significance ($p<0.05$)

Out of 80 cases, 48 out of 72 patients in mild poisoning and 21 out of 72 patients in moderate poisoning, 3 out of 72 patients has survived without intubation and 4 out of 6 patients in moderate poisoning and 2 out of 6 patients in severe poisoning had respiratory depression and survived with intubation and 2 out of 2 patients in severe poisoning have died.

Figure17: Association of Dreisbach'S Classification and clinical outcome

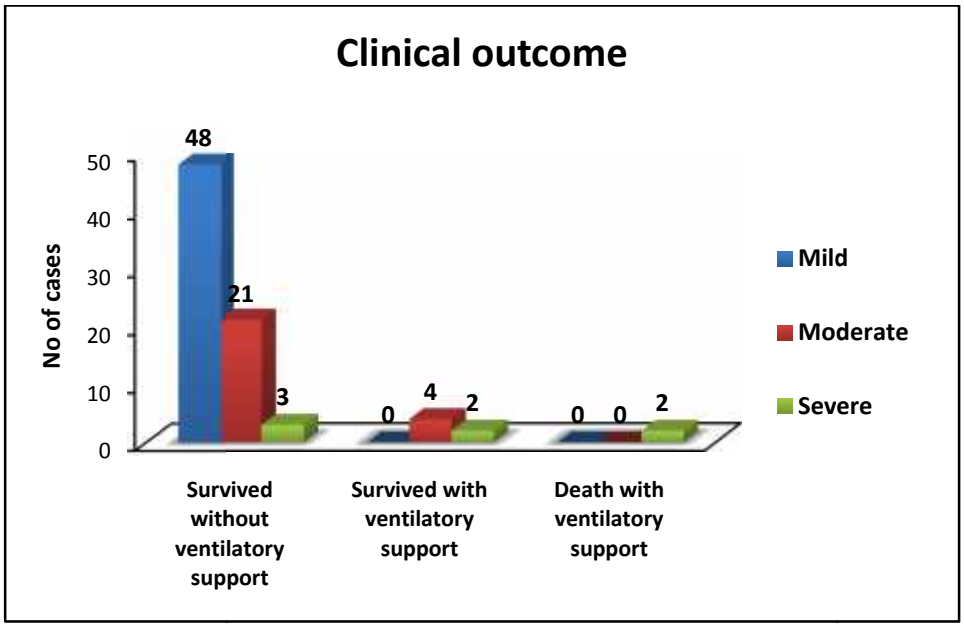


Table 22: Descriptive statistics of biochemical prognostic parameters

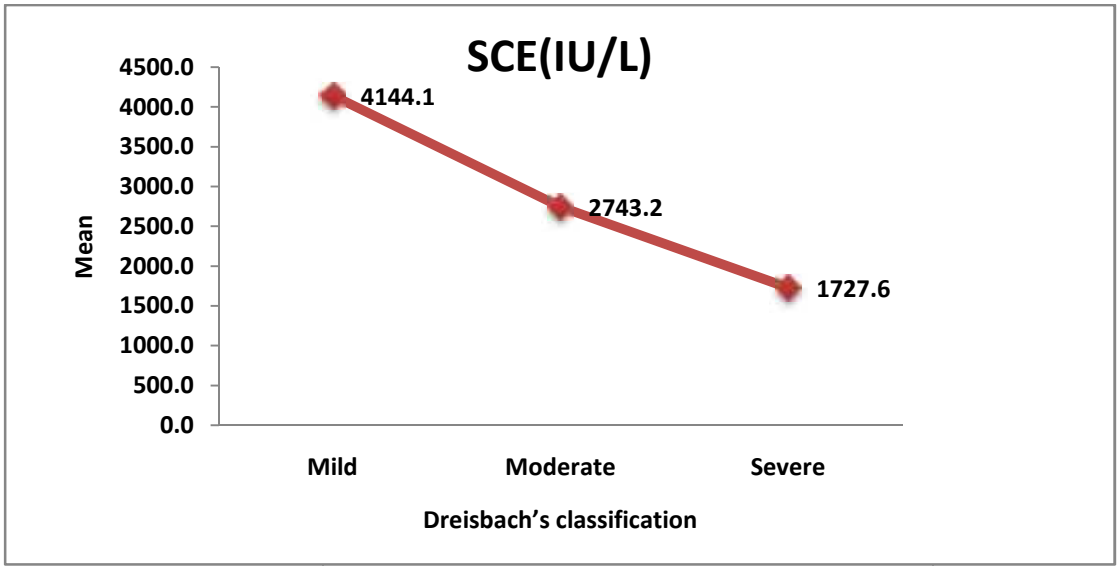
Descriptive Statistics	Minimum	Maximum	Mean	SD
SCE(IU/L)	70	19491	4548.0	3390.8
CPK TOTAL	24	1989	264.4	328.6
SGOT	12	181	29.9	25.8
SGPT	10	142	24.4	21.8

Table 23: Association of Dreisbach'S Classification and mean biochemical prognostic parameters

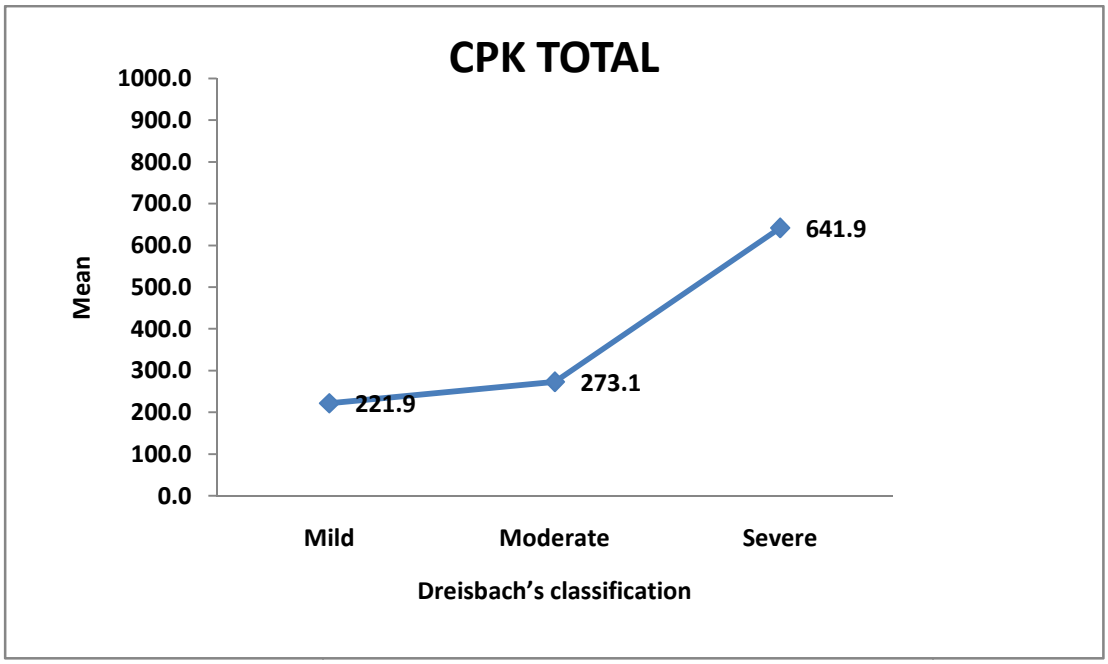
Parameters	Mild		Moderate		Severe		ANOVA
	Mean	SD	Mean	SD	Mean	SD	p value
SCE(IU/L)	4144.1	3465.7	2743.2	1730.7	1727.6	2585.0	0.003*
CPK TOTAL	221.9	203.9	273.1	371.1	641.9	677.5	0.008*
SGOT	24.8	11.4	27.8	21.6	72.1	59.6	0.001*
SGPT	19.4	9.4	21.5	11.1	69.1	49.8	<0.001*

Note: *means significant at 5% level of significance ($p<0.05$)

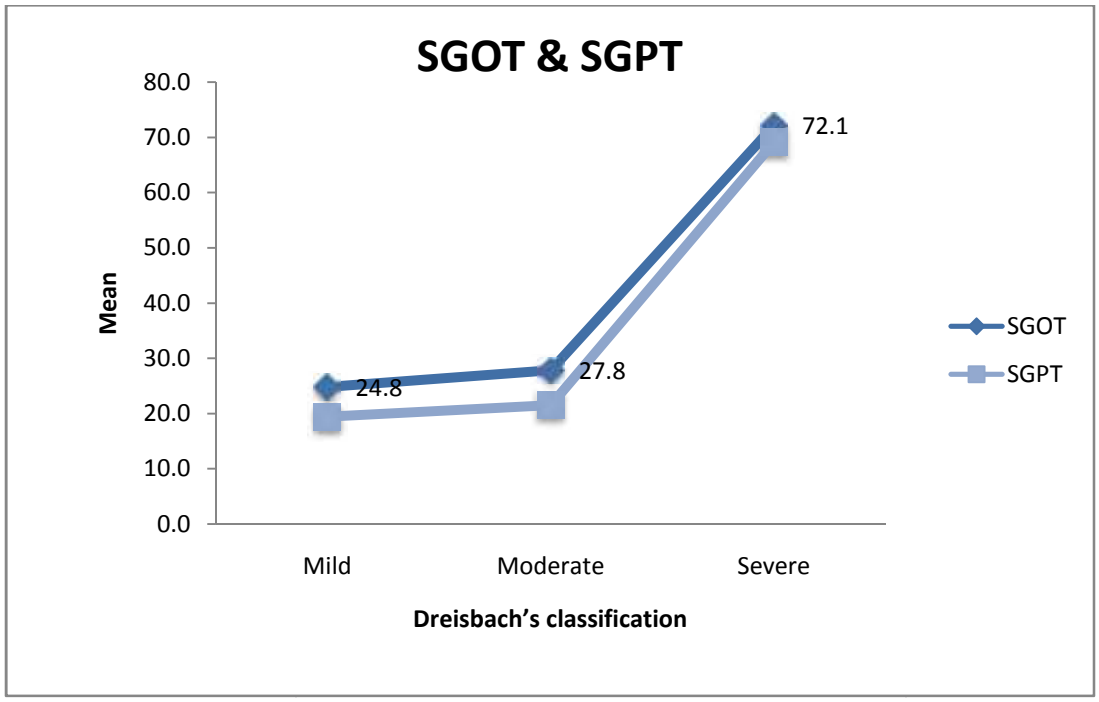
Figure 18: Association of Dreisbach'S Classification and mean Biochemical prognostic parameters

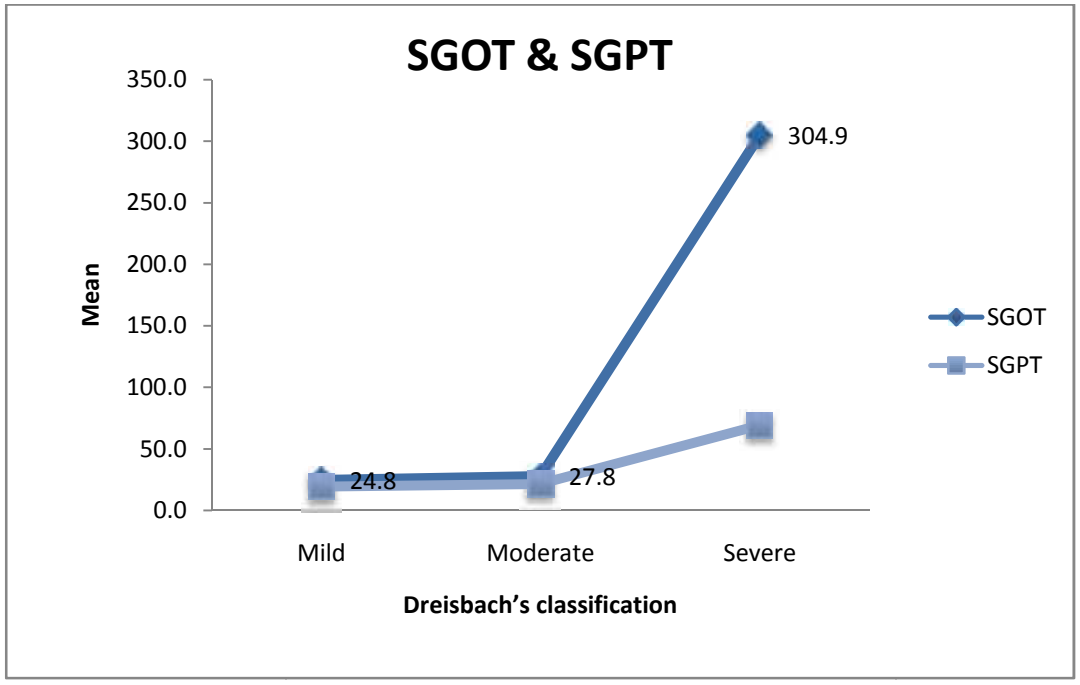


The mean pseudo cholinesterase level in mild, moderate and severe poisoning were 4144.1, 2743.2 and 1727.6 respectively. It was found to be statistically significant.



The mean CPK levels in mild, moderate and severe poisoning were 221.9, 273.1 and 641.4 respectively. It was found to be statistically significant.





The mean SGOT and SGPT levels mild and moderate poisoning were found to be normal limits.

DISCUSSION

In India, the most common used pesticide in agriculture is Organophosphorus compound and it has become one of the major health issues especially in developing countries because of their easy availability and wide use of pesticides.[94]

In our study, the incidence of OP poisoning is higher in the age group of 21-30 years (38.8%), followed by 23.8% in the age group 11-20 years. This is consistent with the study done by Bhattacharyya et al[2] which showed that most commonest age group is 21-30 years and also in Mcihammet G et al[119]. But in the study done by Hassan NAM et al[120] the common age group is 11-20 years. As we can see the most common group of affected individuals are among youngsters and the reason may be because these individuals are vulnerable to various emotion conflicts that occur during this phase of life.

Majority of the patients in our study were females which accounting for 51.3% 41 cases and males were 39 cases 48.8%. This is consistent with Murat S et al[121] study with female predominance and also in the study done by Hassan NAM et al[120] with 51.7% were males and 48.3% were males. But in Bhattacharyya et al[2] study 66.6% were males and 33.3% were females.

The commonest mode of poisoning was suicidal in nature. This accounts for 98.8% in our study and most common route of exposure was oral route. This is similar with the study done by Murat et al[121].

In our study, majority of OP poisoning were among farmers (35%) and most of them were illiterates (63.8%).

India is an agrarian country with around 70% of the people depending directly or indirectly upon agriculture with higher incidence of OP poisoning is seen in rural areas than in urban population which accounts for 61.3 % and 38.8%. This is consistent with Dalal et al[122] and Otto et al[123] respectively.

The most common compound used in our study is Malathion and Monocrotphos 27.5% each followed by Dichlorvas 16.3%. In study done by Murat et al[121] Dichlorvas was commonest compound where as in Karalliedde L et al8 study dimethoate was common compound consumed among OP patients.

The mean pseudocholinestrase levels in mild, moderate and severe poisoning cases were 4144.1, 2743.2 and 1727.6 respectively. The mean CPK levels in our study in different grades of poisoning were 221.9, 273.1 and 524.4. These CPK levels are similar with the study conducted by Bhattacharyya et al[2], SenR et al[1], Eun-Jung Kang, Su-Jin Seok , Kwon-Hyun Lee et al[114], Kale BS et al[116], Vijayakumar PG et al[117], Eizadi Mood N et al[118] respectively.

Our study revealed that changes in serum creatine kinase and its raised level were associated with (6 patients) respiratory failure and (2 patients) death. 4 out of 21 patients with moderate poisoning required ventilator support and 2 of 7 patients with severe poisoning required ventilator support. Early onset respiratory failure is seen within 24 hours of exposure in 5 patients this may be due to cholinergic over activity such as increased salivation, increased sweating, increased bronchial secretions, pinpoint pupil, depressed level of consciousness and respiratory failure.

Only 1 patient had late onset respiratory failure i.e after 24 hours of exposure this may be attributed to respiratory infection. Average arterial blood gases values of these patients were P^H- 7.24 (range 6.98-7.40), Pco_2-40.6mmhg (range 20-51mmhg), Po_2-68.6(50-98mmhg), Hco_3-14.4(range 10-24mmol/l), Sao_2- 88.6% (range 84-98). The duration of mechanical ventilation was 6.2+/- 7.4 days.

2 patients with mechanically ventilated in severe poisoning died of cardio respiratory arrest following myocardial infarction and pneumonia and their abnormal laboratory values were elevated liver, renal and cardiac enzymes with hyperglycemia and elevated triglycerides. Total duration of all the respiration failure patients were 16.6+/-7 days.

In our study patients who developed respiratory failure their initial CPK level were above 250 and patient who died, their CPK levels were 1441 and 1116 which is consistent with the study done by Bhattacharyya et al[2].

High serum levels of creatine kinase at admission indirectly indicated the severity of poisoning and these correlations are found to be statistically significant. We also found that high initial CPK level is associated with higher rates of respiratory failure requiring endotracheal intubation and mechanical ventilation and higher mortality.

In the present study mean levels of liver enzymes are within normal range in cases without complications as well as cases with respiratory failure and deaths. There is no much increase in liver enzymes in these groups. This is consistent with the study done by AB Patel et al[111] and there is slight impairment of the liver enzymes in a study done by

Antonio F Fernandez et al[112] but overall these findings are consistent with no clinical significant hepatotoxicity.

In our study, we found that high initial serum CPK levels is associated with severe degree of poisoning and is associated with complications and mortality and the results were statistically significant.

Complications like respiratory failure in 6 patients, pneumonia in 3 patients, acute kidney injury in 2 patients, convulsions in 1 patient and myocardial infarction in 1 patient.

CONCLUSION

To conclude, serum creatine kinase should be used as an alternate biomarker and considered as a routine investigation in order to predict the respiratory failure and its outcome of OP poisoning severity.

SUMMARY

This was a prospective study of 80 patients admitted with consumption of Organophosphorus compound poisoning at _____ _____from November 2015 to June 2017.

This study was carried out to know the changes in levels of serum creatine kinase and liver enzymes with its severity of poisoning and its prognosis.

The patients were in the age group 15 to 58 years and the mean age group is 29.5 years. Majority of patients belonged to the age group 21 – 30 years and comprised 38.8% of study population. 51.3% of the patients were females. Route of exposure of poison was oral and was suicidal in nature in majority of the patients. The most common compound used was Malathion 27.5% followed by Monocrotphos 26.25%.

48 out of 80 (60%), 25 out of 80 (31.3%) and 7 out of 80 (8.8%) were considered as mild moderate and severe cases of poisoning in our study. The mean Pseudocholinesterase levels were 4144.1, 2743.2 and 1727.6 (IU/L) in mild, moderate and severe cases of poisoning.

The mean CPK levels 221.9, 273.1 and 524.4. IU/L in mild and moderate cases of poisoning. CPK level was found to be elevated (1441 and 1116 IU/L) in fatal cases.

This study showed that there was a high degree of correlation between the initial serum CPK levels and the severity of OP poisoning. These correlations are found to be statistically significant ($p<0.001$).

High initial CPK level is associated with need for endotracheal intubation and mechanical ventilation and more chances of mortality. We observed that mean CPK levels was highest in death group followed by patients who survived with intubation. The results were statistically significant ($p<0.001$).

To conclude, serum CPK can be used as an alternative biomarker in assessing severity of OP poisoning and can predict the prognosis.

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ANNEXURES I

ETHICAL CLEARANCE CERTIFICATE

ANNEXURES II

CONSENT FORM

INFORMED CONSENT FORM **:** **"**STUDY OF LEVELS OF SERUM CREATINE PHOSPHOKINASE AND LIVER ENZYMES AS A PROGNOSTIC INDICATORS IN ACUTE ORGANOPHOSPHORUS POISONING"

GUIDE :

P.G.STUDENT :

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is to assess the levels of serum creatinekinase and liver enzymes in organophosphorus poisioning.

PROCEDURE:

I understand that I will undergo detailed history and clinical examination and investigations.

RISKS AND DISCOMFORTS:

I understand that there is no risk involved in this study and I may experience mild pain during the above mentioned procedures.

BENEFITS:

I understand that my participation in this study will help to assess the levels of serum creatinekinase in organophosphorus poisoning.

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulation of hospital. If the data is used for publication the identity will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw from study at any time.

INJURY STATEMENT:

I understand in the unlikely event of injury to me during the study I will get medical treatment but no further medical compensation.

(Signature of Guardian) (Signature of patient)

STUDY SUBJECT CONSENT FORM:

I confirm that has explained to me the purpose of research, the study procedure that I will undergo and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant/ Guardian Date

_____ _____

Witness to signature Date

ANNEXURE III

STUDY PROFORMA

PATIENT INFORMATION

NAME: **CASE NO. :**

AGE: **IP NO. :**

SEX: **DOA:**

ADDRESS: **DOD:**

OCCUPATION:

CHIEF COMPLAINTS:

HISTORY OF PRESENT ILLNESS:

PAST HISTORY:

HISTORY OF HYPERTENSION

HISTORY OF IHD

HISTORY OF TUBERCULOSIS

HISTORY OF DIABETES MELLITUS

HISTORY OF MALIGNANCY

HISTORY OF HEPATIC OR RENAL DISEASE

HISTORY OF BLOOD TRANSFUSION

HISTORY OF COPD/ASTHMA

POISONING

COMPOUND

AMOUNT

TIME OF CONSUMPTION

PERSONAL HISTORY

SMOKING

ALCOHOLISM

GENERAL PHYSICAL EXAMINATION

VITALS

PULSERATE:
BLOOD PRESSURE:
RESPIRATORY RATE:

SYSTEMIC EXAMINATION

RESPIRATORY SYSTEM
CARDIOVASCULAR SYSTEM
CENTRAL NERVOUS SYSTEM
PER ABDOMEN

INVESTIGATIONS

Hemoglobin	gm%
Total WBC Counts	Cells/mm^3
ESR	mm after 1 hour

URINE EXAMINATION

Albumin	
Sugar	
Microscopy	

CHEST X-RAY

ECG

BIOCHEMISTRY

SERUM ELECTROLYTES:

SERUM CHOLINESTERASE:

SERUM CREATINE KINASE:

LIVER FUNCTION TEST:

FINAL DIAGNOSIS

OUTCOME

SURVIVED WITHOUT VENTILATORY SUPPORT

SURVIVED WITH VENTILATORY SUPPORT

DEATH WITH VENTILATORY SUPPORT

KEY TO MASTER CHART

D.O.A	-	Date of admission
SCE	-	Serum cholinesterase
CPK TOTAL	-	Creatine Phosphokinase
D.O.A	-	Date of discharge
OP	-	Organophosphorus

ANNEXURES IV

MASTER CHART

MASTER CHART														
Sl. No	IP NO	D.O.A	NAME	AGE	SEX	ROUTE OF EXPOSURE	COMPOUND	SCE(IU/L)	CPK TOTAL	SGOT	SGPT	D.O.D	OP DETECTECTED	CLINICAL OUTCOME
1	1577	15.1.16	SHRUTHI MALLAPPA	22	F	ORAL	MONOCROTPHOS	6550	45	19	17	21.1.16	Y	survived without ventilatory support
2	1764	18.1.16	VITTAL SANGAPPA	55	M	ORAL	MONOCROTPHOS	423	178	24	18	24.1.16	Y	survived without ventilatory support
3	2244	19.1.16	TIPPANNA B PUJARI	24	M	ORAL	DICHLOROVAS	9188	114	29	30	26.1.16	Y	survived without ventilatory support
4	2248	20.1.16	BAGAPPA AMASIDDA PUJARI	25	M	ORAL	DICHLOROVAS	3890	163	27	37	27.1.16	Y	survived without ventilatory support
5	3010	27.1.16	SAVITRI	35	F	ORAL	PHOSPHONIC ACID	296	98	24	19	28.1.16	y	survived without ventilatory support
6	4084	5.2.16	MAHESH	30	M	ORAL	CHLORPYRIPHOS	8171	421	41	33	25.2.16	Y	survived with ventilatory support
7	4111	5.2.16	HONAMMA	26	F	ORAL	MONOCROTPHOS	7964	55	14	13	12.2.16	Y	survived without ventilatory support
8	4332	8.2.16	NAGAPPA	38	M	ORAL	PARATION	7298	73	32	57	16.2.16	Y	survived without ventilatory support
9	4399	8.2.16	AKTAR BANU	35	F	ORAL	MONOCROTPHOS	745	118	25	18	15.2.16	Y	survived without ventilatory support
10	4404	8.2.16	ANASUYA	25	F	ORAL	MONOCROTPHOS	1145	138	21	10	11.2.16	Y	survived without ventilatory support
11	4637	10.2.16	ASHWINI	19	F	ORAL	TRIZOPHOS	5820	66	18	21	17.2.16	Y	survived without ventilatory support

12	4902	12.2.16	VIDYASHREE	22	F	ORAL	MALATHION	5992	57	22	26	18.2.16	Y	survived without ventilatory support
13	5075	13.2.16	MALLAMA	25	F	ORAL	MALATHION	8699	188	22	19	20.2.16	Y	survived without ventilatory support
14	10538	30.3.16	SAHADEV	45	M	ORAL	DIMETHOATE	404	435	38	24	5.4.16	Y	survived with ventilatory support
15	10882	1.4.16	INDUMATHI	20	F	ORAL	MALATHION	2826	100	35	34	9.4.16	Y	survived without ventilatory support
16	11247	4.4.16	PREETHI	18	F	ORAL	MALATHION	5151	120	27	20	17.4.16	Y	survived without ventilatory support
17	11862	9.4.16	SUJATHA	38	F	ORAL	PHORATE	616	50	23	27	16.4.16	Y	survived without ventilatory support
18	13525	22.4.16	SHILPA	19	F	ORAL	TRIAZOPHOS	8355	131	20	15	28.4.16	Y	survived without ventilatory support
19	13622	23.4.16	SUKUDEV	50	M	ORAL	MONOCROTPHOS	130	138	16	11	30.4.16	Y	survived without ventilatory support
20	13651	24.4.16	KASHINATH	25	M	ORAL	METHYLEPARATHION	5407	30	16	12	30.4.16	Y	survived without ventilatory support
21	15240	7.5.16	PRAVEEN	28	M	ORAL	DICHLORVAS	11865	45	24	20	15.5.16	Y	survived without ventilatory support
22	16629	18.5.16	SWETHA	18	F	ORAL	MALATHION	5516	229	73	79	24.5.16	Y	survived without ventilatory support
23	16657	19.5.16	RAJBI	31	F	ORAL	MALATHION	8162	77	23	21	27.5.16	Y	survived without ventilatory support
24	16984	22.5.16	RENUKA	16	F	ORAL	MONOCROTPHOS	5732	28	25	26	28.5.16	Y	survived without ventilatory support
25	17459	22.5.16	SHANTAMMA	56	F	ORAL	PROPHENOFUS+CYPERMETHRIN	6359	59	19	10	26.5.16	y	survived without ventilatory support
26	17745	27.5.16	SUBBAWWA	45	F	ORAL	METHYLPARATHION	8116	105	22	11	2.6.16	y	survived without ventilatory support
27	18484	3.6.16	DAREPPA	30	M	ORAL	METHYLPARATHION	6879	70	26	12	8.6.16	Y	survived without ventilatory support
28	19491	12.6.16	SHOBA	25	F	ORAL	MALATHION	19491	129	19	11	20.6.16	Y	survived without ventilatory support
29	19501	12.6.16	SANGANNA	35	M	ORAL	MONOCROTPHOS	8353	320	34	33	18.6.16	Y	survived without ventilatory support

30	20287	18.6.16	NINGAPPA	16	M	ORAL	CHLORPYRIPHOS	137	331	18	13	24.6.16	Y	survived without ventilatory support
31	20498	20.6.16	VISHWANATH	38	M	ORAL	MONOCROTPHOS	322	483	23	14	18.7.16	Y	survived with ventilatory support
32	22625	9.7.16	PREETHI	15	F	ORAL	MALATHION	4139	24	126	43	17.7.16	Y	survived without ventilatory support
33	23427	16.7.16	LAXMI	19	F	ORAL	DICHLOROVAS	2006	218	13	16	24.7.16	Y	survived without ventilatory support
34	24241	24.7.16	LAXMI CHANMALLAPPA	27	F	ORAL	MALATHION	4138	157	22	16	30.7.16	Y	survived without ventilatory support
35	25268	1.8.16	SUNIL	31	M	ORAL	DICHLOROVAS	726	182	25	20	9.8.16	Y	survived without ventilatory support
36	25824	6.816	IRRANNA	35	M	ORAL	MONOCROTPHOS	140	500	108	117	22.8.16	Y	survived with ventilatory support
37	26553	11.8.16	SIDDU	25	M	ORAL	DICHLOROVAS	726	204	84	45	17.8.16	Y	survived without ventilatory support
38	26634	12.8.16	SOMILIBAI	45	F	ORAL	MONOCROTPHOS	7901	136	45	18	18.8.16	Y	survived without ventilatory support
39	27021	15.816	PARVATHI	28	F	ORAL	MONOCROTPHOS	5235	156	19	20	21.8.16	Y	survived without ventilatory support
40	27584	19.8.16	BHIMAPPA	21	M	ORAL	DICHLORVAS	5879	1441	16	13	19.8.16	Y	Death with ventilatory support
41	27762	21.8.16	GURURAJ	24	M	ORAL	DICHLORVAS	8730	359	18	20	15.9.16	Y	survived with ventilatory support
42	28987	30.8.16	CHANNAPPA	45	M	ORAL	MONOCROTPHOS	369	148	30	30	4.9.16	Y	survived without ventilatory support
43	1613	16.1.17	SANGEETHA	25	F	ORAL	MALATHION	4930	63	23	18	23.1.17	Y	survived without ventilatory support
44	2055	19.1.17	DUDAPPA	32	M	ORAL	DICHLOROVAS	7479	515	20	15	26.1.17	Y	survived without ventilatory support
45	2414	22.1.17	GURUANNA	48	M	ORAL	MONOCROTPHOS	105	231	82	83	29.1.17	Y	survived without ventilatory support
46	2644	22.1.17	LAXMI JYOTEPPA JYOTHI	22	F	ORAL	MONOCROTPHOS	1666	1150	28	14	AMA 25.1.17	Y	survived with ventilatory support
47	3081	28.1.17	IBRAHIM	20	M	ORAL	MALATHION	3081	181	25	15	5.2.17	Y	survived without ventilatory support

48	3320	30.1.17	MADHUMATHI	15	F	ORAL	MALATHION	5821	241	34	26	5.2.17	Y	survived without ventilatory support
49	3503	31.1.17	KUSAPPA	20	M	ORAL	MALATHION	5768	119	36	42	7.2.17	Y	survived without ventilatory support
50	3657	1.2.17	ANJANA PRAVEEN PUJARI	21	F	ORAL	MALATHION	4484	48	20	15.6	8.2.17	Y	survived without ventilatory support
51	4668	10.2017	SHIVANAND YALLAPA KOLLI	35	M	ORAL	MALATHION	6087	190	16	12	19.2.17	Y	survived without ventilatory support
52	4769	11.2.17	SANGAPPA DAREPPA	46	M	ORAL	MONOCROTPHOS	6988	55	16	12	17.2.17	Y	survived without ventilatory support
53	4956	13.2.17	TARA SIDDAPPA DOSAMANI	18	F	ORAL	MALATHION	3422	229	12	14	17.2.17	Y	survived without ventilatory support
54	5579	19.2.17	SURESH IRAPPA	40	M	ORAL	MONOCROTPHOS	5970	270	31	10	26.2.17	Y	survived without ventilatory support
55	5759	20.2.17	CHANDRASHEKAR	24	M	ORAL	DICHLOROVAS	5193	173	26	19	27.2.17	Y	survived without ventilatory support
56	5992	22.2.17	GANGUBAI CHANDU	50	F	ORAL	MONOCROTPHOS	5235	63	28	15	1.3.17	Y	survived without ventilatory support
57	6242	24.2.17	MANGALA PARESAPPA	47	F	ORAL	MALATHION	4179	205	29	18	2.3.17	Y	survived without ventilatory support
58	6928	3.3.17	SHANTAWWA BHIMMAWA	58	F	ORAL	DIMETHOATE	5488	1116	23	17	11.3.17	Y	Death with ventilatory support
59	7453	7.3.17	DADASAB MUDRASAB	30	M	ORAL	DICHLORVAS	4903	312	17	13	15.3.17	Y	survived without ventilatory support
60	7706	9.3.17	DANISH RAJASHEKAR	25	M	ORAL	PROPHENOFUS+CYPERMETHRIN	152	71	18	14	16.3.17	Y	survived without ventilatory support
61	7892	10.3.17	MOUNESH	17	M	ORAL	MALATHION	3562	134	18	32	16.3.17	Y	survived without ventilatory support
62	14505	6.5.17	BHUVANA LACHU CHAVAN	16	F	ORAL	MALATHION	4262	96	19	20	16.5.17	Y	survived without ventilatory support
63	14634	8.5.17	GEETHA SANTOSH PUJARI	26	F	ORAL	DICHLOROVAS	1989	158	181	142	16.5.17	Y	survived without ventilatory support
64	14950	10.5.17	GURUBAI	16	F	ORAL	MALATHION	5619	206	36	21	16.5.17	Y	survived without ventilatory support
65	15040	11.5.17	IRRANAGOUDA SHARANAGOUDA	28	M	ORAL	MALATHION	4458	108	20	12	17.5.17	Y	survived without ventilatory support

66	15079	11.5.17	PARVATHI NINGAPPA	36	F	ORAL	QUINPHOS	244	191	14	13	17.5.17	Y	survived without ventilatory support
67	15140	12.5.17	VIDHYASREE	22	F	ORAL	MALATHION	2385	137	26	20	24.5.17	Y	survived without ventilatory support
68	15240	13.5.17	SUBASH CHANDRA BOSE	30	M	ORAL	DICHLOROVAS	818	95	20	12	20.5.17	Y	survived without ventilatory support
69	15702	17.5.17	SUREKHA CHANDKOTI	25	F	ORAL	DIMETHOATE	4635	63	13	14	25.5.17	Y	survived without ventilatory support
70	15899	19.5.17	BHIMRAY	35	M	ORAL	MONOCROTPHOS	115	42	26	13	26.5.17	Y	survived without ventilatory support
71	17017	27.5.17	POOJA	23	F	ORAL	UNKNOWN COMPOUND	6446	107	25	20	3.6.17	Y	survived without ventilatory support
72	17236	29.5.17	SUKUDEV	34	M	ORAL	DIMETHOATE	7221	159	13	10	4.6.17	Y	survived without ventilatory support
73	17764	2.6.17	REVANASIDDAPPA	42	M	ORAL	PHENYLPHYRAZOLE	7628	182	20	15	AMA 5.6.17	y	Survived without ventilatory support
74	18115	6.6.17	BANDENAWAZ	45	M	ORAL	DICHLOROVAS	6670	171	35	49	8.6.17	Y	survived without ventilatory support
75	18210	6.6.17	AKSHATA P TANGADGI	20	F	ORAL	MONOCROTPHOS	5638	101	16	21	10.6.17	Y	survived without ventilatory support
76	18485	8.6.17	VAISHALI ANIL LOKHANDE	19	F	ORAL	DICHLOROVAS	1648	246	16	11	19.6.17	Y	survived without ventilatory support
77	18825	12.6.17	KUMAR D BANDIWADDAR	21	M	ORAL	DICHLOROVAS	283	146	15	19	22.6.17	Y	survived without ventilatory support
78	19152	14.6.17	MACHINDRA N PAWAR	18	M	ORAL	DICHLOROVAS	70	156	24	13	21.6.17	Y	survived without ventilatory support
79	19702	18.6.17	KASHINATH K BIRADAR	28	M	ORAL	MONOCROTPHOS	5267	253	34	20	21.6.17	Y	survived without ventilatory support
80	19576	17.6.17	MAHADEVI SINDHUR NAIK	32	F	SKIN CONTACT	MONOCROTPHOS	5770	128	16	10	21.6.17	Y	survived without ventilatory support