"GLYCEMIC STATUS AT THE TIME OF PRESENTATION IN ACUTE ORGANOPHOSPHOROUS POISONING AND ITS CORRELATION WITH SEVERITY AND CLINICAL OUTCOME"

BY

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Dissertation submitted to the

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ABBREVIATIONS

OP	-	Organophosphorous
WHO	-	World Health Organisation
Ach	-	Acetylcholine
NMJ	-	Neuro muscular junction
Hr	-	Hour
Mg	-	milligrams
PNS	-	Peripheral nervous system
%	-	Percent
LD_{50}	-	Lethal Dose
RR	-	Respiratory rate
AchE	-	Acetylcholinesterase
HR	-	Heart rate
BP	-	Blood pressure
AF	-	Atrial fibrillation
TSH	-	Thyroid stimulating hormone
CN	-	Cranial nerve
IMS	-	Intermediate syndrome
DPN	-	Delayed polyneuropathy
BchE	-	Butryl cholinesterase
ABG	-	Arterial blood gas
LFT	-	Liver function tests
Yrs	-	Years

ABSTRACT

Background:

Acute Organophosphorus poisoning (OP) is prevalent in the world and its numbers are constantly on the rise.[1]World Health Organisation (WHO) has estimated that nearly 2 lakh die from pesticide poisoning in the world. In India, it is the most common poisoning and exposure to OP compounds in the form of nerve agents and pesticides poses an ever ending threat[2].India has about 60-80% of rural population. Thus, pesticides are routinely used for state-of-the-art farming and are readily available over the counter. Therefore a pesticide is an easy source for lethal purposes.[3]

Aim: Glycemic status at the time of presentation in acute organophosphorous poisoning and its correlation with severity and clinical outcome

Objectives:

1. To assess the glycemic status by estimating random blood glucose level at the time of admission in cases of acute organophosphorous poisoning.
2. To assess severity of the poisoning with Peradeniya Organophosphorus poisoning scale
3. To correlate the documented blood glucose levels and serum pseudo cholinesterase levels with the severity and clinical outcome

Methodology:

Cross sectional observational study was undertaken in a confirmed OP poisoning case. 100 confirmed cases were studied thoroughly including the presence of respiratory failure, detailed assessment of CNS and cardiovascular examination.

All patients were given stomach wash, body and eye wash, in patients who had exposure via uncovered skin and / or eyes. This was followed by 1 gm bolus dose of PAM (Pralidoxime) by slow IV injection. Thereafter, a bolus dose of atropine (2 mg

iv push) was administered after correcting cyanosis, till signs of atropinisation (clear lungs, dry axilla, dry mucosa, heart rate ≥ 100 bpm, and dilated pupils). All patients were monitored closely and continuously and all clinical signs assessed 12th hourly till complete recovery and were followed till discharge from hospital. Various necessary investigations were done at the time of admission and later throughout the hospital stay. In our study we correlated the glycemic status and pseudocholinesterase levels.

Results:

Mortality rate of 28% was observed in patients with hyperglycaemia which was highly significant ($p<0.05$). The results indicate RBS value >160mg/dl is a good marker for predicting the mortality and also for assessing the need for ventilator support. Admission RBS was comparable to the drop in pseudo cholinesterase levels, with a $p=0.004$ which was highly significant.

Conclusion:

Hyperglycemia can occur in moderate to severe organophosphorous poisoning.

The occurrence of hyperglycaemia correlates with complications, requirement of ventilator support and poor prognosis. Hyperglycemia is also correlated with low levels of pseudocholinesterase in predicting mortality and ventilator support. In conclusion admission RBS > 160 mg/dl can be considered as a prognostic factor in predicting the morbidity and mortality of organophosphorous poisoning

KEYWORDS:

Glycemic Status ,Organophosphorous Poisoning, Pseudocholinesterase.

TABLE OF CONTENTS

SL. NO	CONTENTS	Page Number
1	INTRODUCTION	01
2	OBJECTIVES	02
3	REVIEW OF LITERATURE AND BASIC SCIENCES	03
4	METHODOLOGY	50
5	OBSERVATION AND RESULTS	53
6	DISCUSSION	73
7	CONCLUSION	79
8	SUMMARY	80
9	BIBILOGRAPHY	81
10	ANNEXURES	
	I. ETHICAL COMMITTEE CLEARANCE CERTRIFICATE	94
	II. INFORMED CONSENT FORM	95
	III. CASE PROFORMA	99
11.	KEY TO MASTER CHART	103
12.	MASTER CHARTS	104-105

LIST OF TABLES

Sl. No	TABLES	Page Number
1	Common effects of acute OP toxicity based on receptors	19
2	Difference between IMS and DPN	25
3	Interpretation of cholinesterase levels	28
4	Treatment of organophosphate exposure	40
5	Distribution of patients according to age(yrs)	53
6	Distribution of patients according to gender	54
7	Distribution of patients according to occupation	55
8	Distribution of patients according to route of poisoning	56
9	Distribution of patients according to motive of poisoning	57
10	Distribution of patients according to quantity of consumption	58
11	Distribution of patients according to time interval	59
12	Distribution of patients according to symptoms	60
13	Distribution of patients according to RBS at time of admission	61
14.	Distribution of patients according to admission Pseudocholinesterase levels	62
15.	Distribution of patients according to RR	63
16.	Distribution of patients according to HR	64
17	Distribution of patients according to complications	65
18	Distribution of patients according to ventilator support	66
19	Association between RBS and complications	67

20.	Association between Cholinesterase and complications	68
21.	Association between RBS and Cholinesterase	69
22.	Association between RBS and ventilator support	70
23.	Association between cholinesterase and ventilator support	71
24.	Distribution of patients according to OUTCOME	72
25	Studies comparing age group	73
26	Studies comparing gender	74
27	Studies comparing motive of poisoning	74
28	Studies comparing mode of poisoning	75
29	Studies comparing clinical features	75
30	Studies comparing complications	76
31	Studies comparing hyperglycemia	76
32	Studies comparing Pseudocholinesterase levels	77

LIST OF GRAPHS

Sl. No.	Graphs	Page Number
1	Distribution of patients according to age(yrs)	53
2	Distribution of patients according to gender	54
3	Distribution of patients according to occupation	55
4	Distribution of patients according to route of poisoning	56
5	Distribution of patients according to motive of poisoning	57
6	Distribution of patients according to quantity of consumption	58
7	Distribution of patients according to time interval	59
8	Distribution of patients according to symptoms	60
9	Distribution of patients according to RBS at time of admission	61
10	Distribution of patients according to admission Pseudocholinesterase levels	62
11	Distribution of patients according to RR	63
12	Distribution of patients according to HR	64
13	Distribution of patients according to complications	65
14	Distribution of patients according to ventilator support	66
15	Association between RBS and complications	67
16	Association between Cholinesterase and complications	68
17	Association between RBS and Cholinesterase	69
18	Association between RBS and ventilator support	70
19	Association between cholinesterase and ventilator support	71
20	Distribution of patients according to OUTCOME	72

LIST OF FIGURES

Sl. No.	Figures	Page Number
1	Schematic diagram of PNS and sites of Ach	04
2	Sites of action of chemical transmitters at the nerve impulse	05
3	Mechanism of action of OP compounds	16

INTRODUCTION

Acute Organophosphorus poisoning (OP) is prevalent in the world and its numbers are constantly on the rise.[1]

World Health Organisation (WHO) has estimated that nearly 2 lakh die from pesticide poisoning in the world. In India, it is the most common poisoning and exposure to OP compounds in the form of nerve agents and pesticides poses an ever ending threat[2].

India has about 60-80% of rural population. Thus, pesticides are routinely used for state-of-the-art farming and are readily available over the counter. Therefore a pesticide is an easy source for lethal purposes.[3]

They have been imported in India since 1951, but no one knew the fatality of these compounds, till the Kerala food poisoning tragedy in 1958.This tragedy lead to the death of more than 100 people due to inadvertent stocking of food stuff and folidol packages in the same container leading to contamination of food stuff.[4]

Organophosphorus insecticides inhibit acetylcholinesterase causing accumulation of acetylcholine (Ach) at central and peripheral cholinergic nerve endings, including neuromuscular junctions (NMJ). OP poisoning is treated by lavage, antidotes, an anticholinergic, an oxime-pralidoxime and respiratory support.[5]

In literature, following OP poisoning hyperglycaemia has been reported. Non-Ketotic hyperglycaemia can also develop.[6]

Mortality rate is 7-12%. Death is usually as a result of respiratory paralysis.[7]hence this study aims at studying random blood sugar (RBS) values in patients who were not known diabetic individuals, before consuming OP compounds, at admission as a prognostic indicator and to correlate it with pseudo cholinesterase levels.

AIMS AND OBJECTIVE OF THE STUDY

AIM:

Glycemic status at the time of presentation in acute organophosphorous poisoning and its correlation with severity and clinical outcome

OBJECTIVES:

1. To assess the glycemic status by estimating random blood glucose level at the time of admission in cases of acute organophosphorous poisoning.
2. To assess severity of the poisoning with Peradeniya Organophosphorus poisoning scale and level of serum Pseudocholinesterase and to correlate the documented blood glucose levels and serum pseudocholinesterase levels with the severity and clinical outcome.

REVIEW OF LITERATURE

HISTORICAL CONSIDERATIONS:

One of the most potent anticholinesterase inhibitors tetraethyl pyrophosphate (TEPP) is synthesized by Moschnin around 1850 and first written account of it dates back to 1854 by De Clermont.[8]

Around 1936-37 German scientist Gerhard Schrader also noticed identical effect during his work and developed a technique for TEPP production on a commercial scale. Pervasive work by Schrader on these compounds during the world war II lead to the synthesis of around 2000 compounds like parathion, systox, tabun, sarin etc.[8,9]

The meiotic properties of TEPP were noticed by Schrader and its cholinesterase inhibiting activity was validated by Gross. The word "cholinesterase" was introduced by Stedman and team in 1932.Comprehensive work done by them has established that there are two main types of cholinesterase that is acetyl-cholinesterase, acetocholinesterase or true cholinesterase and non-specific cholinesterase or pseudo cholinesterase.[8]

During search for compound which can reactivate the cholinesterase inhibited by organophosphorous, Jandorf and Summerson found hydroxylamine can nullify these compounds. David and Wilson et al introduced PAM (pyridine-2-Aldoxime) as reactivator.[8]

Functional system of the autonomic nervous system:

The portion of the nervous system which controls the visceral functions of the body is called autonomic nervous system. This helps in control of arterial pressure, gastro-intestinal motility, secretions, urinary bladder control, sweating and

body temperature etc. Autonomic nervous system centres are located in the hypothalamus, brain stem and spinal cord.

Sympathetic: Spinal cord - T1 - L1. Pre - vertebral ganglia - celiac and hypogastric

Parasympathetic: From central nervous system - III, VIII, IX, X cranial nerves. Spinal cord - S2, S3 and S4 nerves.[10]

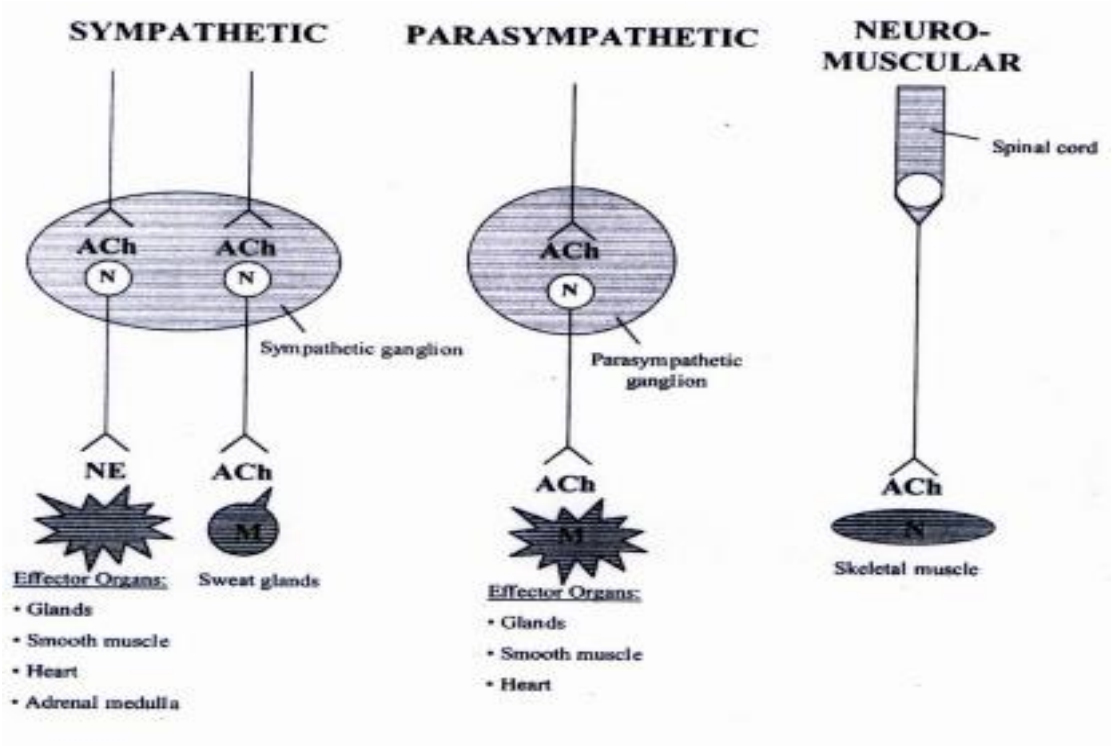


Fig. 1: Schematic diagram of peripheral nervous system and sites of acetylcholine (ACh) action M, muscarinic cholinergic receptors; N, nicotinic cholinergic receptors; NE, nor epinephrine.

Neurotransmitters[10, 11, 12, 13]:

1. Nor-epinephrine (NE) is the neurotransmitter for preganglionic sympathetic neurons (adrenergic).
2. At the preganglionic neurons, Ach is the neurotransmitter for both sympathetic and parasympathetic autonomic nervous system along with postganglionic neurons. Hence they are called as "cholinergic" neuron**s.**

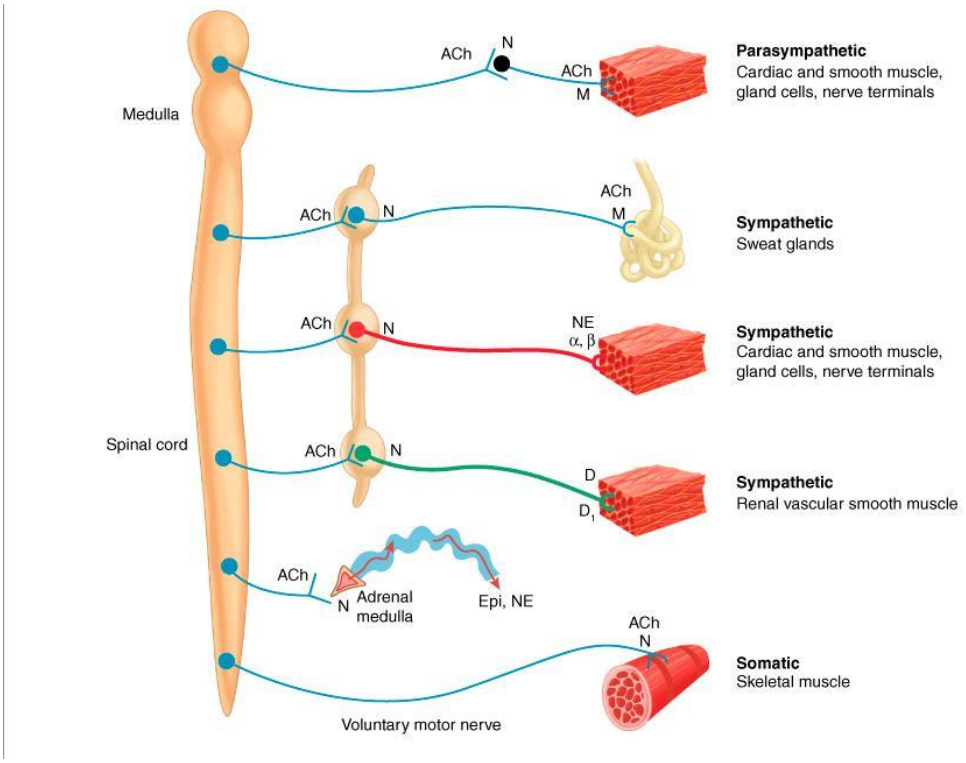


Fig. 2: The sites of action of chemical transmitters at the nerve impulse.

ANATOMY & PHYSIOLOGY OF N.M. JUNCTION[10]

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 synthesized at

a) Autonomic effector sites innervated by postganglionic parasympathetic fibres.
b) Preganglionic autonomic fibres of sympathetic and parasympathetic ganglion cells and adrenal medulla.
c) Motor end-plates on skeletal muscle
d) Certain synapses in central nervous system

Ach in the motor nerve terminal is synthesized in axoplasm from choline and CoA by a process facilitated by the enzyme choline acetyl transferase. The choline necessary for this is derived from Extra Cellular Fluid which is transported into the nerve terminal by a carrier mediated transport system.

(Choline Acetyl transferase)

Choline + Acetyl-Co A ----------► Acetylcholine

About 20% of Ach in nerve terminal is present as free Ach in the axoplasm, and 80% is contained within the vesicles, each containing about 4-5 x 10^5molecules of Ach.

Separate pools or stores of Ach exist within the nerve terminal. Most of the Ach (80%) can be released by nerve impulses (the releasable pool), but some cannot (the non-releasable pool or stationary pool).

The releasable pool consists of the Ach contained within the vesicles, whereas non-releasable pool is the Ach of the axoplasm. Releasable pool is often divided into immediately available and the reserve pool.

Acetylcholine acts through two receptors: [11, 12]

MUSCARINIC RECEPTORS

Muscarine is a poison derived from toadstools that activates only muscarinic receptors. Effector cells are stimulated by postganglionic neurons of the parasympathetic nervous system and also postganglionic cholinergic neurons of the sympathetic nervous system.

NICOTINIC RECEPTORS

Nicotine will activate the nicotinic receptors in pre and post ganglionic neurons of both the sympathetic and parasympathetic systems and also in the membranes of skeletal muscle fibers at neuromuscular junction.

Metabolism of Acetyl choline:

Junctional acetyl cholinesterase is the enzyme liable for the hydrolysis of Ach in the synaptic cleft.

Acetyl cholinesterase is a protein at the basement membranes of the muscles, motor end plates and the nerve terminals. Each molecule of the enzyme is capable of binding and hydrolyzes several molecules of acetylcholine.

It has been estimated that for each molecule of Ach released by a nerve impulse, there are at least 10 active enzymes sites available.

This arrangement ensures that each Ach molecule only reacts once with the receptor, after which it is rapidly (in < 1msec) hydrolysed.[10]

CLASSIFICATION AND BIOLOGICAL ASPECTS OF OP COMPOUNDS:

All OP compounds share a very similar chemical structure. Their central part is a phosphorous atom with a double bond to either oxygen (P = O) or sulphur (P = S) and has 3 side chains.

One side chain, the X group or leaving group, differs widely between the OP agents and determines many of its physical and chemical characteristics. The two other side chains, the R_1 and R_2groups, are typically alkoxy groups but can also be any aliphatic or aromatic hydrocarbon.

These side chains differ between each individual OP agents and are responsible for variability in their toxicokinetics. Compounds with a sulphur atom (P = S) instead of an oxygen atom (P = O) bound to the phosphorus core are known as phosphorothioates or organothiophosphorus compounds.

Such agents have weak inherent toxicity on their own but are metabolized into an OP (oxon) metabolite (P=O) with much greater toxicity. Malathion and parathion are two common examples of phosphorothioates; their active metabolites are malaoxon and paraoxon respectively.

OP compounds are either solids or liquids. Solid compounds can be used as powder insecticide, but more commonly they are dissolved in a liquid hydrocarbon vehicle for application.

The hydrocarbon vehicle enhances the compound's adhesion to and penetration through the insect exoskeleton, and improves its environmental persistence on crops or plants after application. Thus most commercially available OP products are oily liquids. Whereas some are odourless, many are described as having a garlic-like or kerosene odour of varying strength.

Most OP compounds decompose rapidly in the environment by photolysis or hydrolysis. The environmental half-life for most products is relatively short, typically ranging from hours to days, although some can persist for weeks.

Toxic dose: [9]

The toxicity of OP compounds varies widely, based on the specific agent, route of administration and duration of exposure, and patient specific factors such as genetic differences in OP metabolism and enzyme susceptibility to the agent.

The most potent OP compounds are chemical weapons (e.g., sarin, soman, tabun, VX).[15] Commercial agricultural OP products also have a high toxicity. Animal and household OP products are typically less potent.

An agent's relative toxicity is generally expressed as a measurement of its lethal dose in experimental animals (LD_{50}).

CLASSIFICATION AND BIOLOGICAL ASPECTS OF OP COMPOUNDS:

Classification[4, 16]:

Organophosphorus compounds are classified as -

I. By chemical structure into alkyl phosphates and aryl phosphates

A. Alkyl phosphates:

- HETP (Hexaethyl tetra phosphate)
- TEPP (Tetraethyl pyrophosphate) tetron, fosvex etc
- OMPA (Octamethyl pyrophoramide) schardan
- Dimefox [Bis(dimethyl amino) fluorophosphine oxide]
- Isopestox [bis (isopropylamino) fluro phosphine oxide] pestox
- Malathion [5,(1,2 dicarbethoxyehyl) 0, o dimethyl dithiophosphate]
- Sulfoteppa (tetra ethyl 0, dithiopyrophosphate) – dithione Asp-47 ;

- Systox, demeton (0,0 diethyl 10-2 ehtylmercapto ethyl thionophosphate)
- Dipterex (0,0 dimethyl 2-2-2 trichorol hydroxyl ethyl phosphate)-tug orbait

B. Aryl phosphates:

- Paroxon (0,0, diethyl-o-p-nitrophenyl phosphate) –E 600-mintacol
- Parathion (0, 0, diethyl-o-p-nitrophenyl thiosulphate or diethyl thiophosphoric ester of p-nitrophenol)-folidol (bayer), Eketox (sandoz), kilphos, niran, rhyntox, oriental Bug's bait etc.
- EPN-o, (ethyl-o-p nitrophenyl benzene thionophsophate), EPN 300.
- Methyl parathion (o, o-dimethyl o-p nitrophenyl thiophsophate), metacide.
- Chlorothin-o, o-dimethyl, (o-3-chloro-4-nitrophenyl) thiophosphate
- Diazion (o, o-diethyl-o-(2-isopropyl-6-methyl-4-pyrmidyl) thiophosphate – Tik 20.
- Methyl umbelliferone (o,o diethyl thiophosphate)

II. By toxicity:[9]

Highly toxic (LD_{50}< 50mg/kg)

- Azinophos-methyl (Cruthion)
- Bomyl (Swat)
- Carbophenthion (Trithion)
- Chlorfenvinphos (Birlane)
- Chlormephos (Dotan)
- Coumaphos (Co-ral)
- Cyanofenphos (Surecide)

- Demeton (Systox)
- Dialifor (Torak)
- Dicrotophos (Bidrin)
- Disulfoton (Diasyston)
- EPN
- Famphur (Bo-ana, warbex)
- Phenamiphos (Nemacur)
- Fenophos phan (Agrifox)
- Isophenfos (Amaze, oftanol)
- Isoflourphate
- Mephosfolan (Cytolane)
- Methamidophos (Monitor)
- Methidathion (Supracide)
- Mevinphos (Phosdrin)
- Monocrotophos (Azodrin)
- Parathion – ethyl
- Parathion methyl (Penncap-M)
- Tetraethylpyrophosphate (Bladan, TEPP, Tetron)

Moderate Toxicity (LD_{50} = 50-1000mg/kg):

- Acephate (Orthene)
- Bensulide (Betasan)
- Chloropyrofos (Durshan, Lorsban)
- Crotoxyphos (Ciodrin)

- Cythioate (Proban)
- DEF (De-Green, E-Z off D)
- Deneton-s-methyl (Metasystox)
- Diazinon (Basudin, Spectracide)
- Dichlorvos (DDVP, Vapona)
- Dimethoate (Cygon)
- Edifenphos (EDDP)
- Ethion (Nialate)
- Ethoprop (Mocap)
- Fenitrothion (Accothion)
- Fenthion (Anthio)
- IPB (Kitazin)
- Leptophos (Phosvel)
- Merphos (Folex)
- Naled (Dibrom)
- Phosalone (Zofos)
- Phosmet (Imidan, prolate)
- Pirimiphos-ethyl (Dipterex, Dylox, Fernex)
- Profenofos (Curacron, Polycron, Selecron)
- Propetamphos (Safrotin)
- Pyrazophos (Afugan, curamil)

Low toxicity (LD_{50} = > 1000mg/kg):

- Bromophos (Nexagan)
- Etrimfos (Ekanet)

- Iodofenphos (Nuvanol N)
- Malathion (Cythion)
- Phoxim (Baythion)
- Prophylthiopyrophosphate (Aspon)
- Temephos (Abate, Abathion)
- Tetrachlorrinphos (Gardona, Rabon)

(LD_{50} = lethal dose in experimental animals)

MODE OF INTOXICATION [9, 14]**:**

Exposure to OP insecticides can occur by any route. Occupational exposures occur via direct dermal or mucous membrane contact or by inhalation. Most OP insecticides are not volatile, so exposure by the respiratory route is generally the result of inhalation of aerosolized droplets. Occasionally, accidental exposures may occur with ingestion of contaminated foodstuffs. Intentional exposures are typically ingestions or parenteral injections of OP compounds.

Most OP compounds are remarkably lipo-philic. Hence they are readily absorbed by passive diffusion across lungs, GI system or skin. Deliberate ingestion is common in developing countries, where they are readily available.

ORGANOPHOSPHORUS COMPOUND METABOLISM[9, 17, 18, 19]:

OP agents are widely distributed to various tissues, especially the liver, kidneys, adipose, and lipid rich tissues, where they are accumulated and persist for weeks.

Most OP agents are biological available, but the phosphorothioates (P=S), such as Malathion and parathion, require bio activation. They undergo oxidative desulfuration, primarily by the cytochrome P-450 system, to form an oxon (P=O) metabolite that possesses much greater toxicity. The process of bio activation can slow the onset of effects after exposure.

Elimination is mainly via urine and faeces. Urinary and faecal elimination is usually rapid; 80-90% of the compound is excreted within 48 hrs. Some compounds remain longer in body like fenthion and Fenithrothion.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS: [20, 21]

OP compounds are cholinesterase inhibitors and exert their toxicity by interfering with the function of Ach, an essential neurotransmitter throughout the autonomic and central nervous system.

Organophosphates are powerful inhibitors of carboxylic ester hydrolases including chymotrypsin, acetylcholinesterase, pseudocholinesterase, plasma and hepatic carboxylesterases (aliesterases), paraoxonases (A-esterases), and other nonspecific proteases.

Functioning acetylcholinesterase is present in nervous tissue and skeletal muscles and is also expressed on the membrane of erythrocytes.

The active acyl pocket in the centre of acetylcholinesterase is a narrow cleft 2 nm deep and surrounded by tetramers. Two additional sites on the enzyme include a

peripheral anionic site and a choline subsite of the active centre. These three sites confer the steriospecificity for other ligands to bind.

At the base of the cleft, the enzymatic active site contains a serine 203 residue. Coiled nearby are histidine 447 residue and glutamate 334. When Ach enters the binding area, it is attracted by local atomic forces into a tetrahedral structure with the serine, histidine, and glutamate, and forms a nucleophilic serine hydroxyl intermediate.Ach is hydrolyzed to acetic acid and choline, which then leaves the site and enzyme, and reforms its allosteric structure. Turnover time for this reaction is 150 microsecondS[20].

Although OP compounds differ structurally from acetylcholine, they can bind to the acetylcholinesterase molecule at the active site and phosphorylate / phosphonate the serine moiety. The resultant conjugate is far more stable than the acetylcholine-acetylcholinesterase conjugate, although endogenous hydrolysis does occur.

Depending upon the amount of stability and charge distribution, the time to hydrolysis is increased. Phosphorylated or phosphonylated enzymes, degrade over days to weeks, making the acetylcholinesterase essentially inactive. In order for the physiologic enzyme activity to return, new enzyme must be generated or antidote to be given.[21]

Once the acetylcholinesterase is phosphorylated, over the next 24 to 48 hours, an alkyl group is eventually lost from the conjugate, further exacerbating the clinical situation. As this ‘ageing’ occurs the enzyme can no longer spontaneously hydrolyze and gets permanently inactivated.[20]

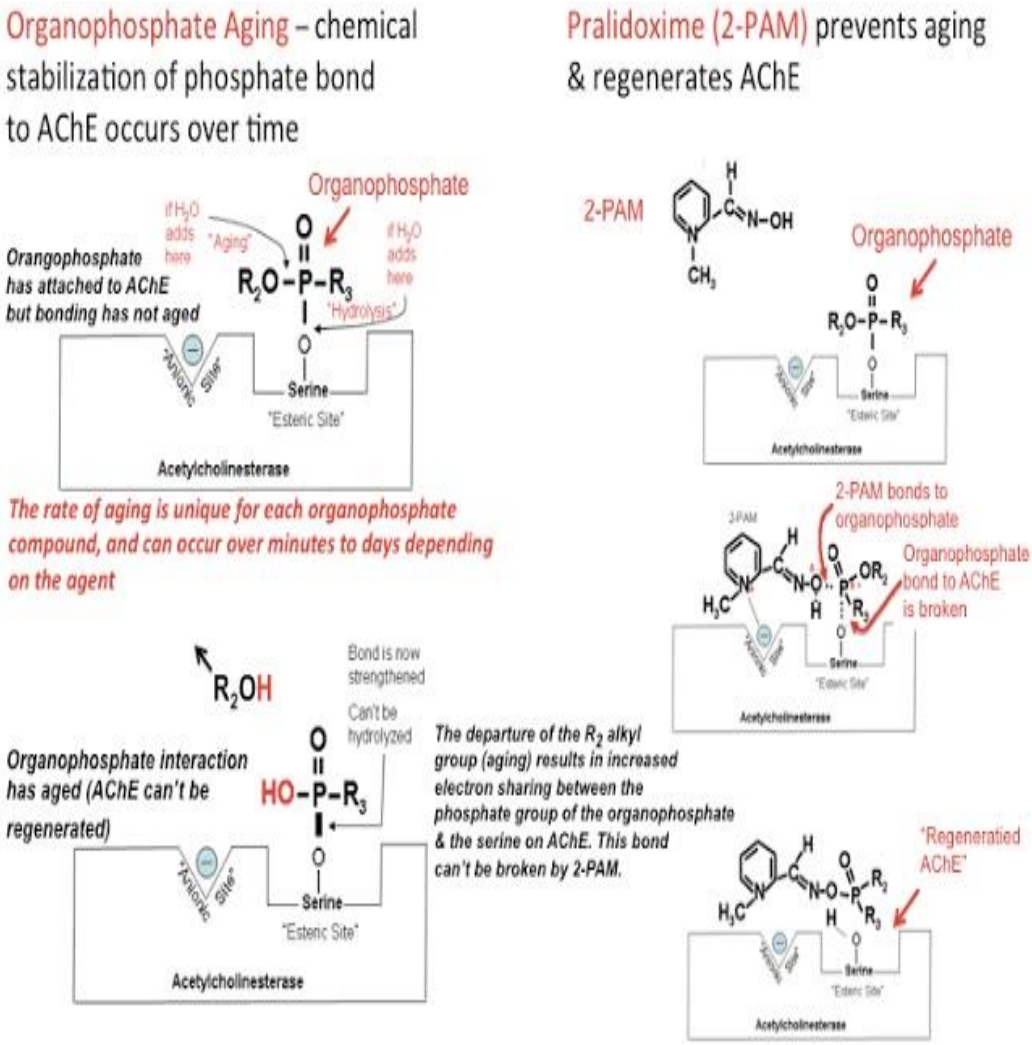


Fig. 3: Mechanism of action of OP compound

CLINICAL FEATURES:

The presentation of an OP exposure depends on

- specific agent
- quantity and
- Route of entry.

Symptoms typically occur immediately after exposure but may be delayed depending on the agent and rate of ingress. Onset of symptoms occur rapidly with inhalation and slower with dermal exposure.[23]

Most commonly symptoms appear within 30 minutes to 24 hrs of exposure. Therefore, symptoms which occur 24 hrs after exposure cannot be attributed directly to acute organophosphate poisoning.[24, 25]

Local effects:

GI symptoms appear first before the onset of systemic symptoms. The immediate local effects are on eyes and the respiratory tract.

Ocular effects include meiosis, conjunctival hyperemia, heaviness in and behind the eyes and dimness of vision.

The respiratory manifestations are rhinorrhoea, nasal hyperaemia, tightness in chest, prolonged expiration and increased bronchial secretion.[24, 25]

Systemic Effects:

Significant exposure to OP insecticides can result in 4 major clinical syndromes

A) Acute toxicity:

Acute toxicity typically occurs after a single exposure when a significant threshold level of cholinesterase inhibition has been reached. Typically, this occurs when 30% to 50% of AChE has been inhibited, although the %e varies widely between individuals but more important is the rapidity with which this inhibition occurs.[26]

Most patients develop symptoms within 6 hours. Patients remaining asymptomatic for 12 hrs after ingestion are unlikely to develop major clinical toxicity.[27]

Exception exist with some highly lipophilic OP compounds (most common - fenthion) which produce only subtle cholinergic features initially then progressive muscle weakness including respiratory failure requiring intubation for several days.[28]

Clinical effects by receptor type: Poisoning typically represents a dynamic mixture or balance of muscarinic and nicotinic systems.**[29, 30, 31, and 32]**

Muscarinic	Nicotinic
Peripheral Gastrointestinal Salivation Increased gastrointestinal motility Abdominal cramping/discomfort Vomiting Diarrhoea Faecal incontinence Ocular Meiosis Blurred vision Lacrimation Respiratory Rhinorrhea Bronchorrhea Bronchospasm Dyspnoea Coughing Hyperventilation Hypoxemia Cardiac Bradycardia/bradydysrhythmias Cardiac conduction delays Hypotension Genitourinary Urination Urinary incontinence Dermal Sweating Central nervous system (nicotinic central nervous system receptors may also play a	Neuromuscular Muscular fasciculations / twitching Cramps Weakness Hyporeflexia Paralysis Hypoventilation Excessive sympathetic output (from stimulation of postganglionic sympathetic neurons and adrenal catecholamine release) Mydriasis Tachycardia Hypertension

small role) Agitation Confusion Hallucinations Somnolence Ataxia Coma Respiratory depression Seizures	

Table 1: Common effects of acute OP toxicity based on receptors Clinical effects on each organ system

Cardiac effects: [33, 34, 35]

Increased HR and BP occur initially and decreased HR and BP in the later stages. Most common sign is tachycardia. Late onset bradycardia is due to direct action on myocardium by organophosphorus compound. Hypertension is due to the combined effect of vasoconstriction from stimulation of sympathetic ganglia and also nor adrenaline release from adrenal medulla. Hypotension may also occur due to muscarinic action or blocking of ganglia by hyperpolarisation.

Cardiac manifestations such as AF, conduction blocks and ventricular fibrillation occur in later stages.

ECG changes are sinus bradycardia, right axis deviation, AV Block, ST segment depression and T wave inversion in all leads. Due to metabolic and electrolyte disturbances, can also lead to myocardial injury, autonomic dysfunction and asynchronous repolarisation producing variable QRS complexes and RR interval.

Respiratory effects: [36, 37, 38]

- Rhinorrhea
- Excessive nasopharyngeal and bronchial secretions
- Pulmonary oedema
- Decreased breath sounds on auscultation.
- Bronchoconstriction resulting in chest tightness, coughing, wheezing

The combination of excessive secretions and narrowed airways can rapidly lead to inadequate gas exchange. This is aggravated by a concomitant CNS depression or diaphragmatic weakness. Thus, respiratory failure is the most common cause of death in patients with severe OP poisoning.

Neurologic effects: [23, 29, 30,31,39,40]

- Anxiety, giddiness, restlessness, emotional liability, slurred speech, ataxia, seizures, drowsiness, confusion, difficulty in concentration, headache, insomnia, excessive dreaming, apathy, tremors, lethargy, coma, negative reflexes,
- Depression of respiratory and circulatory centres which leads to Cheyne - Stokes respiration, dyspnoea, hypotension and cyanosis.

GI Effects: [42, 43\]

Salivation, excessive oropharyngeal secretions, nausea, vomiting, abdominal discomfort, diarrhoea or loss of faecal continence, and hyperactive bowel sounds.

Ocular effects [30, 31]:

- Meiosis
- Blurred vision
- Lacrimation
- Mydriasis(occasionally)

Altered immunity to infection: [23]

Direct action of Ach on the immune system or by toxic chemical stress associated with cholinergic poisoning might lead to severe cholinergic stimulation causing immunosuppression.

Effects on temperature regulation: [23]

Incidence of deranged temperature regulation seen in the form of hypothermia is 7%. Few might experience fever lasting for many days, this is a biphasic response.

Vocal card paralysis [23]: In few patients vocal card paralysis was also reported.

Changes in metabolism and endocrine activity[6, 23, 29,44,45,46]:

Transient hyperglycaemia and glycosuria might occur in severe OP poisoning. It is differentiated from diabetic coma by the absence of acetone bodies.

The diurnal pattern of plasma adrenocorticotrophic hormone can change. Nicotinic receptors in brain might increase the release of several pituitary hormones such as vasopressin, prolactin and adrenocorticotrophic hormone.

A decrease in the level of thyroxin and triiodothyroxine and an increased secretion of TSH was also noticed. Hyper amylasaemia and acute pancreatitis may be seen.

B) Delayed neuromuscular effects (Intermediate syndrome):[24, 47, 48,49,50,51,52,53,54]

Intermediate syndrome is defined as muscle paralysis which occurs after the apparent recovery from the cholinergic crisis but before the conventional onset of delayed polyneuropathy.[116]

IMS is a type II paralysis which was first described by Wadia et.al [47] in 1974[48]. Symptoms are of acute onset, seen 24-96hrs after poisoning, mainly targeting conscious patients without fasciculations or other cholinergic manifestations.

Incidence of IMS in admitted patients is 10% to 50%.

The mechanism of IMS is likely due to postsynaptic NMJ dysfunction. It is more common in few agents such as Malathion, parathion, fenthion, diazinon, methylparathion, diamethoate; monocrotophos. It might be due to the redistribution of highly lipophilic agents from adipose tissues as blood levels fall or due to fat breakdown.

The main symptoms include muscle weakness, predominantly the proximal limb muscles and neck flexors. Muscles innervated by CN III, VII and X are also affected. Respiratory paralysis is the most lethal complication if not treated early.

Patients are typically conscious with prevailing anxiety, sweating and restlessness due to progressive hypoxia. Weakness of neck flexors and unable to raise the head from the pillows were seen consistently along with moderate to severe weakness of shoulder abduction and hip flexion, but the sparing of distal muscles gives a feeling that the limbs were spared.

Spasticity of limbs, hyperreflexia and dystonia are observed but fasciculations are uncommon. No sensory impairment seen.

Respiratory insufficiency develops within 6 hrs. Initially, the patients seem fine because of use of accessory muscles of respiration. But slowly progress showing tachypnoea, sweating, restlessness and later cyanosis. If not ventilated patients soon becomes unconscious and later death.

If adequate ventilatory support is given, usually a thorough recovery is seen within 4-18days. Function at the neuromuscular junction may be modified for almost 2 years.

IMS is a result of inadequate oxime therapy. IMS ensue when cholinesterase function is very low but the compound is still detectable in the body.

C) Delayed peripheral neuropathy developing weeks or months after acute exposures: Organophosphate induced delayed peripheral neuropathy (OPIDN) 55, 56, 57

OPIDN occur 1 to 5 weeks after recovery from the initial toxic exposure to an OPcompound. The neuropathy may be either motor or sensorimotor and occurs almost exclusively in patients who have had a clinically significant episode of acute poisoning.

Certain agents have been more frequently implicated, such as triorthocresly phosphate, parathion, fenthion, chlorpyrifos, Malathion, mipafox, merphos, leptophos, cyanophose, and others.

Several outbreaks of OPIDP have occurred in various countries where the poisoning was traced in most instances to accidental contamination or adulteration of cooking oils with mineral oils. Triorthocresyl phosphate was responsible for outbreaks of Jamaican ginger paralysis.

The pathogenesis may be due to the OP-induced phosphorylation and subsequent aging of an enzyme found in nervous tissue, called neuropathy target esterase which plays a major role.

Symptoms include calf pain, later developing distal muscle weakness and paraesthesia of feet and hands. The sensory component is milder than the motor component.

Wasting of distal muscles, particularly the small muscles of the hand and those of the anterior and peroneal compartments of the leg is an inevitable consequence. Pyramidal tract signs are also common. Recovery from OPIDP is variable.

TABLE 2: DIFFERENCE BETWEEN INTERMEDIATE SYNDROME (IMS) AND DELAYED POLYNEUROPATHY (DPN) [24]

	IMS	**DPN**
a. Latent period	1- 4 days	2-3 week
beside of weakness		
Limb muscles	Proximal	Distal
Neck muscles	+	-
Cranial nerves	+	-
Respiratory	+	-
muscles		
c.Electromyogram	Tetanic fade	Denervation
d. Recovery	4-18 days	6-12 months
e. OP agents commonly	Fenthion dimethoate	Methamidophas
involved	monocrotophos.	Trichlorophon
		leptophos.

D) Neurobehavioral and neuropsychiatric effects[58]:

Long-term neurobehavioral symptoms associated with OP exposures include fatigue, anxiety, depression, restlessness or irritability, confusion, and occasionally frank psychosis. Symptoms are usually mild, begin within days to weeks of an exposure and resolve spontaneously over the course of several months to a year.

Diagnosis of Acute OP Poisoning -

- ✓ History of ingestion of the compound,
- ✓ Signs and symptoms,
- ✓ Improvement after atropine and oxime therapy,
- ✓ Decreased cholinesterase levels.[59]

Clinical diagnosis is based on the history of exposure and its characteristic symptoms. Decreased serum or RBC cholinesterase level is useful in the non typical cases (<50%). Based on cholinesterase levels it can be classified into-

- Mild - cholinesterase activity of 20-50%,
- Moderate 10-20% and
- Severe- <10% .[29, 59]

If suspected, treatment to be started immediately even before laboratory confirmation.[29]

DIAGNOSTIC TESTS[9]:

- **Atropine challenge** – A diagnostic aid in patients with suspected OP poisoning.[31] 1-2 mg atropine is administered intravenously (IV) and patient's response is observed. Improvement in patients with muscarinic effects from other causes is seen. If no clinical improvement, then the patient is more likely to have OP poisoning.

- If the agent abused is known, levels can be measured in serum, urinary or tissue.[60]
- Butrylcholineesterase and RBC cholinesterase levels are measured for confirming an OP exposure.RBC cholinesterase activity levels are more specific, and correlate better with the clinical severity than butyl cholinesterase levels.[61]

TYPES OF CHOLINESTERASE: [5, 11, 12, 62, 63]

Two major forms of cholinesterase are present which hydrolyze acetyl choline

1. **Plasma cholinesterase:** (Pseudo/ Butryl Cholinesterase) Found in plasma, liver (main), pancreas and intestinal mucosa. Variations are seen in liver disease, chronic inflammation, malnutrition, morphine, codeine, succinylcholine administration and hypersensitivity reactions.
2. **RBC Cholinesterase**: (True/Specific Cholinesterase) Seen in nervous tissue, erythrocytes, lung, spleen and grey matter. Decreased in pernicious anaemia and post malarial treatment. Measuring acetylcholinesterase is preferred, because it depicts the degree of inhibition of synaptic cholinesterase (acetylcholineesterase).Whereas butryl cholinesterase levels are handier to measure. Butrylcholinesterase shows any prior cholinesterase inhibition even after recovery of acetylcholinesterase activity by pralidoxime.

In severe poisoning, normal levels are achieved after 4 weeks for butrylcholinesterase and 5 weeks for acetylcholinesterase. Regeneration of AchE occurs at approximately 1% per day.

Decreased cholinesterase levels are confirmatory and are expressed as % of normal levels in healthy adults. > 80% suggest no significant absorption. 50 -80% are usually symptomless, might also indicate over absorption. Early symptoms such as discomfort and cold sweats occur at 20-30% normality. Severe poisoning shows almost 5-10%.

TABLE 3: INTERPRETATION OF CHOLINESTERASE LEVELS[22]

	RBC cholinesterase	**Plasma cholinesterase**
Advantages	Better reflection of synaptic inhibition	Easier to assay declines faster
Site	gray matter, RBC, motor end plate	white matter, plasma, liver, pancreas, heart
Regeneration (untreated)	1% per day	25-30% in fist 7-10 days
Normalization (untreated)	35-49 days	28-42 days
Uses	Unsuspected prior exposure with elevated plasma cholinesterase	Acute exposure
Falsely decreased in	Pernicious anaemia, haemoglobinopathies, antimalarial treatment, Oxalate blood tubes.	Liver disease, malnourished, hypersensitivity reactions, drugs, genetic abnormality

ADVANTAGES OF ESTIMATION OF BchE: [59,64,65,66]

- Simpler and more accurate
- Degree of serum cholinesterase activity is directly proportional to severity of manifestations
- Following pralidoxime administration reactivation of serum cholinesterase is slow compared to erythrocyte cholinesterase.
- Plasma can be stored for a week without any decrease in cholinesterase activity.

DISADVANTAGES OF PSEUDOCHOLINESTERASE ESTIMATION: [59,64,65,66]

- Serum cholinesterase levels vary vastly from one individual to another.
- Low cholinesterase levels have been observed in disease states and genetically.
- Cannot be used to assess the effectiveness of PAM therapy since the levels also include any prior cholinesterase inhibition.
- Levels continuously keep changing as the inhibition of the enzyme by inhibitors and spontaneous reactivation is taking place simultaneously.

Other diagnostic Tests:

- Either in acute poisoning or IMS , repetitive nerve stimulation testing is a rising method for assessing the degree of AchE inhibition.[54,67]
- Routine electromyography is a useful tool in interpreting OP induced muscle weakness.
- ABG and pulse oximetry to assess the adequacy of the patient's ventilation.[112]
- Chest X-ray due to the possibility of pulmonary oedema , aspiration and pneumonitis

- ECG due to the risk of dysarrythmias and conduction blocks.
- LFT should be monitored
- Serum electrolytes and renal function in patients with significant fluid loss due to increased secretions.
- Nonspecific laboratory abnormalities that are to be seen -

✓ Increased glucose levels

✓ Increased leukocyte count

✓ Acidosis

✓ Hypokalemia

✓ Mild elevations in AST and LDH

✓ Elevated serum amylase

✓ Elevations in serum creatine kinase

MANAGEMENT:

1. Acute cholinergic crisis: [24,68,69,70] – MEDICAL EMERGENCY

A. First aid

B. Gastric lavage to restrict more absorption

C. Specific antidote therapy –

• Anticholinergic medication -

• Reactivators of AChE –oximes

D. Benzodiazepines

E. Other medications

A. First Aid:

a) Remove patient from contaminated environment.

b) Remove contaminated clothing

c) Scrub skin with soap water

d) Check breathing and circulation

e) Resuscitate if necessary

f) Support vital functions if necessary

- O_2 inhalation
- Lung ventilation
- Ionotropes

g) Anti convulsive therapy if needed

h) Monitoring of vitals, GCS

B. Restrict further absorption:

Gastric lavage: Gastric lavage should be done as soon as the patient reaches the hospital using nasogastric tube with 50-100ml of NS per lavage.

Administer activated charcoal: Initial doses of 60-100gms, followed by 0.25gms to 0.50gms/kg every 1-4 hrs.

C. Specific antidote therapy: Goals of therapy

a) Reversal of cholinesterase block

b) Reversal of chemical abnormalities at the synapse

Achieved by-

a. Anticholinergic drugs such as atropine or glycopyrrolate
b. Reactivation of Acetycholinesterases by oximes

a. Anticholinergic medications:

ATROPINE:

Atropine is a white odourless crystalline powder, occurring in nature only as a racemic mixture of D- and L-hyoscyamine enantiomers. Atropos is the name of one of the three fates of ancient Greek cosmology who was responsible for cutting the thread of one's life, thus ending it.

Atropine occurs naturally in plants such as Atropa belladonna (deadly nightshade, dwale, poison black cherry, belladonna) and in Datura species (jimsonweed, thorn apple). Atropa belladonna originated in Eurasia where it has been used for centuries as an aphrodisiac and hallucinogen as well as a medicine and poison.[71]

Mechanism of action[72]:

Atropine is a competitive antagonist of acetylcholine. It prevents depolarization and thereby nerve conduction by blocking acetylcholine at muscarinic receptors, which are present on the postsynaptic membrane on autonomic synapses in smooth and cardiac muscle, in exocrine glands, and in nerve ganglia.

It has no significant effect on nicotinic receptors. Atropine crosses the blood-brain barrier and the placenta.

Its antimuscarinic activity can effectively reverse muscarinic hyper stimulation in OP poisoning. It therefore antagonizes the OP-induced hyper salivation, bronchorrhea, bronchospasm, bradycardia, hypotension, lacrimation, urinary incontinence, diarrhoea, meiosis, gastrointestinal cramping, emesis, and central nervous system disturbances.

Dosage and method of administration: [23,59,69,73]

For the treatment of cholinergic signs (bronchospasm, bronchorrhea) from any OP agent, a full vagolytic adult dose of 2mg IV is administered. If possible, the patient should be oxygenated before administration to prevent cardiac dysrhythmias. Atropine dose should be repeated every 2 to 5 minutes until drying of airway

secretions and improved respiratory statuses are apparent. Atropine does not treat the muscular weakness and paralysis seen with cholinergic syndrome.

Alternatively atropine can also be given as continuous infusion.

Dose- 30mg in 200ml of NS at the rate of 0.02-0.08 mg/kg/hr , supplemented by giving additional boluses 1-5mg to achieve control of secretions or severe bradycardia when indicated.

Dose should be titrated to maintain adequate atropinisation for at least 24-48hrs.Patient should be observed for 72 hrs after stopping atropine. Atropine should be started if cholinergic symptoms reoccur.

The end point of anti-cholinergic treatment is clearing of secretions from tracheo-bronchial tree and drying of most secretions. Pupillary dilatation is an early response to atropine, but it is not a therapeutic end point.

Atropine need not be stopped if there is tachycardia. Diaphragmatic muscle weakness is not reversible with atropine

Adverse effects: [59, 69, 73]

Atropine causes anticholinergic toxicity i.e. atropism, the typical antimuscarinic symptoms of tachycardia, mental status changes, hyperthermia, visual disturbances, mydriasis, urinary retention, constipation, flushing, and anhydrosis.

GLYCOPYRROLATE[70, 73, 74, 75] **:**

Can also be used in place of atropine in patients with no evidence of altered sensorium or central toxicity. Better control of secretions, lesser tachycardia, and fewer CNS side effects is few advantages over atropine. Unlike atropine, glycopyrrolate does not cross the blood brain barrier and fewer respiratory infections

occur this may be due to better control of secretions, decreased mucous plugs in smaller airways.

Dose: 0.05 mg/kg or 0.25mg repeated every 5-10 minutes until anticholinergic over activity is reversed. Maximum dose is 2.5mg/d.

ii) Reactivation of Acetylcholinesterase by oxime therapy: [23, 59,76,77,78]

Oximes reactivate acetylcholinesterase inhibited by Organophosphorus compounds. Pralidoxime was discovered in the mid 1950s by Wilson and Colleagues, and was soon successfully introduced into clinical practice for patients with parathion poisoning.[113]

Pralidoxime

Pralidoxime and obidoxime are antidotes for organophosphate (OP) insecticide intoxication. It is available as a parenteral solution and also in auto injectors developed to provide self-treatment in the battlefield. In the United States, the pralidoxime (2-PAM Cl) auto injector is packaged with an atropine auto injector in a package known as the Mark 1 kit.

Mechanism of action:

Cholinergic toxicity results from the accumulation of AChE in the synaptic cleft and myoneural junction, causing an increase in the action potentials transmitted to nerve and muscle. The toxicity of OP chemicals can be reversed and the bond between AchE and the OP can be disrupted, allowing normal AChE activity to return. Oximes are less effective at reversing toxicity at muscarinic sites than at nicotinic sites.

Dosage and administration:

Initial adult dose of 2-PAM Chloride is 1gm IV.

Loading dose of 20- 50mg/kg based on symptoms severity (in NS over 30 minutes), followed by a continuous infusion of 10-20mg/kg/hr. Maximum recommended dose is 12gm in 24 hours.

PAM should be administered as soon as possible after diagnosis. Once the phosphorylated enzyme has aged, the phosphate group becomes irreversibly bound to the enzyme and oxime therapy is no longer effective. It is probably more effective if given within 6 hrs of poisoning.

Dosage should be maintained continuously until clinical improvement is established. Because excretion is renal, the dose of pralidoxime should be reduced in patients with renal insufficiency.

Therapeutic response observed is

Regain of consciousness, symptoms disappear, especially weakness and fasciculations within 10-40 minutes. The next dose should be repeated after 1 hr only if muscle weakness persists.

Adverse effects[79] :

- Cardiovascular effects like tachycardia and mild hypertension associated with rapid infusion. Increase in systolic and diastolic blood pressure and inversion of the T wave on electrocardiogram have been described for 2-PAM doses in excess of 30mg/kg.
- Pain at the injection site, and perioral paraesthesia
- Dizziness, headache, drowsiness, and apprehension.
- Gastrointestinal effects include nausea and hepatic enzyme elevation.

- Blurred vision, diplopia and mydriasis have been reported.
- Skin rash may occur.

Maintenance and duration of treatment:

Is usually given for 5 -7days.[24]The therapeutic concentration of the oximes should be maintained to regenerate as much active enzyme activity as possible until the OP compound is excreted.[23]

PAM should be continued as long as nicotinic symptoms persist as residual OP compound can bind to free PAM and decrease its serum levels[68]. Patients who develop IMS, PAM should be administered for long period until they are weaned off from ventilator.[24]Delayed clinical manifestations occur with lipophilic agents like fenthion, chlorfenthion and parathion.[31, 59]

Drug interactions:

Morphine, succinylcholine, aminophylline, reserpine, theophylline, and phenothiazines like tranquillizers should be avoided if patient is on PAM therapy.[73]

Obidoxime-

- Is effective in smaller doses i.e. 250mg IV/IM as a slow bolus or infusion.[59]
- Is more potent cholinesterase reactivating agent than pralidoxime but its toxicity is slightly greater.[24]

D. Benzodiazepines[26, 56]:

Used to control seizures or if patient is irritable. Diazepam neutralizes few CNS-derived symptoms.

E. OTHERS-

1. Magnesium:

Magnesium Sulphate blocks Calcium channels and thus reduces Acetylcholine release. Given in a dose of 4g on first day of admission, it has been shown to decrease hospitalisation period and improve outcomes in patients with OP poisoning.[117]

2. Clonidine:

- Blocks post synaptic muscarinic receptors.
- Transient inhibition of AchE.
- Blocks the release of acetylcholine from central and peripheral cholinergic neurons.[23]

3. Fluoride:

Atropine and sodium fluoride (15mg/kg) are efficient against tabum.[23]

4. Haemoperfusion dialysis is effective in dimeton-s-methyl sulphoxide, dimethate and parathion poisoning.[82]

5. Anisodamine :

Anisodamine is known for its Anti-cholinergic , Anti-oxidant effects while it has also shown to inhibit the activity of Calcium-ATP enzymes and reduce Calcium overload. In a study done in 2014 by Wang et al postulated that Anisodamine can accelerate the process of atropinisation and shorten hospital stay in OP poisoned patients for whom atropinisation cannot be achieved solely through high dose of atropine.[111]

MANAGEMENT OF INTERMEDIATE SYNDROME[59]:

Ventilator support and PAM is the main therapy. Recovering patients may suddenly go into respiratory distress. Therefore all patients should be observed in hospital up to 5 days after poisoning.

Facilities for ventilator care should be made available if early signs of respiratory insufficiency develop i.e.

- Increase in rate of ventilation > 24 cycles per minute
- Use of accessory muscle of ventilation
- Decreased tidal volume
- Reduced PaO_2 < 60 mmHg

Oxygen should be administered in the early stages of respiratory insufficiency.

Diazepam in 10mg IV is given if the patient becomes anxious or restless while on ventilator. Weaning from ventilator is based on spontaneous breathing efforts, frequent ABG.

Oxime therapy initiated during acute cholinergic phase, should be continued until the patient recovers adequate spontaneous ventilation.

Atropine therapy is continued to maintain mydriasis and HR exceeding 100beats/min for some duration as treatment with pralidoxime. Monitoring and care of fluid and electrolyte status is an important part of management as IMS can cause diarrhoea.[2]

Delayed polyneuropathy does not benefit from any specific drug therapy. Physiotherapy benefits muscle weakness.[24]

COMPLICATIONS: [83]

43% of acute intoxication cases lead to complications. In untreated cases death occurs within 24 hours. Respiratory distress is the most common complication following acute OP poisoning.[84]

Early deaths are mainly related to

1) Respiratory failure due to
    - bronchospasm
    - Respiratory paralysis
    - Pulmonary oedema
    - Apnoea due to medullary respiratory centre depression
    - Increased bronchial secretion

2) CNS depression and seizures

3) Ventricular arrhythmias

Late mortality is due to-

1. Respiratory failure along with associated septicaemia, infection, pneumonia
2. Extensive periods of mechanical ventilation and intensive care management.
3. Sudden ventricular arrhythmias, respiratory failure, sudden collapse

PROGNOSIS depends on-

- Dose of the poison and promptness of treatment.
- Irreversible CNS damage due to prolonged anoxia and convulsions.[85]

TABLE 4: TREATMENT OF ORGANOPHOSPHATE EXPOSURE[87]

Decontamination

Gastrointestinal

- If ingest ion occurred within fast 30 to 60 minutes, place nasogastric tube and empty stomach of all contents.
- Administer activated charcoal, 1 g/kg orally, unless emesis prevents this.
- Do not use cathartics, owing lo anticipated diarrhoea.

Dermal

- Remove patient's clothing and discard it.
- Wash patient's skin and hair with copious amounts of soap and water. - Health care workers should wear protective barriers.
- - Masks with eye shield
- - Water-resistant gowns and shoe covers
- - Nitrile or neoprene gloves
- • Tape gloves and shoe covers to gown.
- • Protect environment from contamination.

Treatment

- Establish airway; administer 100% oxygen.
- Establish intravenous access: obtain cholinesterase activity level. • Atropine, 1-2 mg intravenously test dose.
- Double the dose every 5-10 minutes until tracheobronchial secretions are dry and patient can be oxygenated.
- Disregard pupil size change.
- Consider atropine infusion if extremely large doses required (50 mg in 250 mL normal saline, yielding a concentration of 0.2 mg/mL: titrate to effect). *and*
- Pralidoxime (2-PAM or ProtoPAM)"

Load:

- Adult: 1-2 g IV infusion in saline over 15-30 minutes

Further Doses:

- The dose can be repeated in 1 hour and then every 4-8 hours for 24-48 hours, assuming symptoms resolve, Infuse:

- Adult: 500 mg/hr of a 2.5% solution
    - Obtain electromyogram (EMG) after 48 hours if patient remains symptomatic when pralidoxime is weaned or patient exposed to agents implicated in intermediate syndrome. If EMG is abnormal, continue pralidoxime until EMG normalizes.
    - Monitor erythrocyte acetylcholinesterase activity level during pralidoxime therapy if available; otherwise, stop pralidoxime after 24-48 hours and reassess clinical status.
    - After discharge:
    - - Monitor enzyme activity level until normal.
    - Do not allow patient to return to work with occupational exposure to cholinesterase inhibitors until enzyme levels have normalized.
    - Ensure that workplace has been inspected and meets standards.

ENDOCRINE REGULATION OF THE PLASMA GLUCOSE LEVEL.[10, 11, 88]

The following hormones regulate the plasma glucose level, via:

1) INSULIN:

Insulin was first isolated from pancreas in1922 by Banting and Best. It is secreted in response to energy abundance. Excess carbohydrates are stored as glycogen in liver and muscles, remaining that cannot be stored as glycogen are converted under the stimulus of insulin into fats and stored in adipose tissue.

It increases amino acid uptake by cells and conversion of these amino acids into proteins. It inhibits breakdown of the proteins that are already there in the cells.

CONTROL OF INSULIN SECRETION[10]

At the normal fasting level of blood glucose of 80-90 mg/dl, the rate of insulin secretion is minimal 25ng/min /kg (600 micro units / min / kg) of the body weight. If the blood glucose concentration is suddenly increased to a level 2-3 times normal and is kept at this high level thereafter, insulin secretion increases markedly in 2 stages

I stage: Insulin secretion increase almost 10 fold within 3-5 minutes after acute elevation of the blood glucose results from the immediate dumping of preformed insulin from the beta cells followed by decrease (halfway) back towards normal in another 5-10 minutes.

II stage: After about 15 minutes, insulin secretion rises rapidly reaching a new plateau in 2-3 hours, at a rate of secretion even greater than that in initial phase. This results from additional release of preformed insulin and from activation of some enzyme system that synthesizes and release new insulin.

Relationship between blood glucose concentration and insulin secretion rate: [10]

As the concentration of blood glucose rises above 100 mg/dl of blood, the rate of insulin secretion rises rapidly, reaching a peak 10-30 times the basal level at blood glucose concentration between 400-600 mg/dl. Thus the increase in insulin secretion under a glucose stimulus is dramatic both in its rapidity and in the tremendous level of secretion achieved. The turn off of insulin secretion is almost equally as rapid, occurring within minutes after reduction in blood glucose concentration, back to the fasting level.

The response of insulin secretion to an elevated blood glucose concentration provides an extremely important feedback mechanism for regulating blood glucose concentration. That is, the rise in blood glucose increases insulin secretion

and the insulin in turn causes transport of glucose into the liver, muscle and other cells there by reducing the blood glucose concentration toward the normal value.

2. GLUCAGON: [10]

- Microgram of glucagon / kg raises blood glucose concentration approximately 20 mg/dl of blood in about 20 minutes. Therefore glucagon is called as “Hyperglycaemic factor”

Actions:

- Increases glycogenolysis and gluconeogenesis in liver.
- Effect of blood glucose concentration on glucagon secretion is in exactly opposite direction from the effect of glucose on insulin

Decreased glucose from its normal fasting level of about 90mg/dl of blood down to hypoglycemic levels can increase glucagon secretion as well as its plasma concentration several fold. On the other hand increased glucose to hyperglycaemic levels decreases plasma glucagon.

3. SOMATOSTATIN:

The delta cells of the islets of Langerhans secrete the hormone somatostatin which is polypeptide containing only 14 amino acids that has the extremely short half life in the circulating blood, only 2 minutes. Almost all factors related to the ingestion of food will stimulate somatostatin secretion.Viz:

- Increased blood glucose,
- Increased amino acids,
- Increased fatty acids,
- Increased concentration of several of the gastrointestinal tract hormones released from the upper gastrointestinal tract in response to food intake.

In turn somatostatin has multiple inhibitory effects,

- Depresses secretion of both insulin and glucagon,
- Decreases the motility of the stomach, the duodenum and the gall bladder.
- Decreases both secretion and absorption in the GIT,

Overall it prevents rapid exhaustion of the food making it available over a longer period of time.[10]

4. CATECHOLAMINES:

- Activates phosphorylases in liver via beta-adrenergic receptors and increases hepatic glucose output producing hyperglycemia.
- Epinephrine and Nor-epinephrine also liberates free fatty acids into the circulation and epinephrine decreases peripheral utilization of glucose. However the hyperglycemic effect of epinephrine is generally too transient to produce permanent diabetes.[11]
- Epinephrine is especially important in increasing plasma glucose concentration during periods of stress, when sympathetic nervous system is excited.[10]

5. ADRENAL GLUCOCORTICOIDS

- Elevates the blood glucose and produces hyperglycemia. This is brought about by:
- Increase in protein catabolism with increased gluconeogenesis in the liver.
- Increased hepatic glycogenolysis and ketogenesis.
- A decrease in peripheral utilization of glucose relative to the blood level that maybe due to inhibition of glucose phosphorylation.[11]

6. THYROID HORMONES

Increases blood glucose levels by increasing glucose absorption from the intestine. Also by causing hepatic glycogen depletion (probably by potentiating the effects of catecholamines), accelerates degradation of insulin.[11]

7. GROWTH HORMONE

- It decreases glucose uptake into some tissues (anti-insulin effect)
- Increases hepatic glucose output.
- It mobilizes free fatty acids from adipose tissue thus favouring ketogenesis.[11]

SUMMARY OF BLOOD GLUCOSE REGULATION: [10]

In the normal person the blood glucose concentration is very narrowly controlled usually in a range between 80-90 mg/dl of blood in a fasting person each morning before breakfast. This concentration increased to 120 to 140 mg/dl during the first hour or so following a meal but the feedback system for control of blood glucose return the glucose concentration very rapidly back to the control level, usually within 2 hrs after the last absorption of carbohydrates. Conversely, in starvation the gluconeogensis function of the liver provides the glucose that is required to maintain the fasting blood glucose level.

The mechanisms for achieving this high degree control:

- The liver functions as a very important blood glucose buffer system i.e. when the blood glucose rises to a very high concentration following a meal and the rate of insulin secretion also increases, as much as 2/3rd of the glucose absorbed from the gut is almost immediately returned in the liver in the form of glycogen. Then during succeeding hours, when both the blood glucose concentration and the rate of insulin secretion fall, the liver releases

the glucose back into the blood. In this way, the liver decreases the variations in blood glucose concentration by about 3 fold .In fact, in patient with severe liver disease; it becomes almost impossible to maintain a narrow range of blood glucose concentration.

- It is very clear that both insulin and glucagon function as important separate feedback control system for maintaining a normal blood glucose concentration. When the concentration rises to level too high, insulin is secreted, the insulin in turn causes the blood glucose concentration to decrease toward normal. Conversely, a decrease in blood glucose stimulates glucagon secretion, the glucagon then function in the opposite direction to increase the glucose up toward normal. Under most normal conditions, the insulin feedback mechanism is much more important than the glucagon mechanism, but in instances of diminished glucose intake or excessive utilization of glucose during exercise and other stressful situations, the glucagon mechanism is very useful.
- Also in hypoglycaemia, a direct effect of low blood glucose on the hypothalamus stimulates the sympathetic nervous system. In turn, the epinephrine secreted by the adrenal glands causes still further release of glucose from the liver. This too, helps protect against severe hypoglycaemia.
- And finally over a period of hours and days both growth hormone and cortisol are secreted in response to prolonged hypoglycaemia, and they both decreases the rate of glucose utilization by most cells of the body. This too helps to return the blood glucose concentration toward normal.

Importance of blood glucose regulation: [10]

- Glucose is the only nutrient that normally can be utilized by the brain, retina and germinal epithelium of the gonads in sufficient quantities to supply them with their required energy. Therefore it is important to maintain the blood glucose concentration at a sufficiently high level to provide this necessary nutrition.
- Most of the glucose formed by gluconeogenesis during the inter-digestive period is used for metabolism in the brain. Indeed it is important that the pancreas not secrete any insulin during this time, for otherwise the scant supplies of glucose that are available would all go into the muscles and other peripheral tissues, leaving the brain without a nutritive source.
- On the other hand, it is also important that the blood glucose concentration not rise too high for 3 reasons

1. Glucose exerts a large amount of osmotic pressure in the extracellular fluid, and if the glucose concentration rises to excessive values, this can cause considerable cellular dehydration.
2. An excessively high level of blood glucose concentration causes loss of glucose in the urine.
3. This causes osmotic diuresis by the kidneys, which can deplete the body of its fluids and electrolytes.

HYPERGLYCEMIA IN OP POISONING

Hyperglycaemia and glycosuria have been reported in OP poisoning though ketonuria is absent.[5]in 1971, Namba et al reported that in severe OP poisoning transient hyperglycemia and glycosuria occurs which was again proven in 2013 in a study by sudhir et al[120]. Absence of acetone bodies differentiates from diabetic coma, except for coma in diabetic patient due to hyperosmolarity from elevated blood glucose levels.[31]

Earlier it was postulated that acetylcholine accumulation at sympathetic ganglia sites leads to "Pheochromocytoma-like" increases in catecholamine secretion with subsequent development of hyperglycemia, glycosuria and metabolic acidosis in severe cases.

Hyperglycemia has been associated with more complications in literature.[90]

Mechanism of Blood glucose changes in OPP.

Though the changes in blood glucose and amylase are well known, the mechanism is not clear. Probable mechanisms are

- These chemicals inhibit cholinesterase allowing accumulation of acetylcholine at cholinergic sites resulting in continuous stimulation of cholinergic fibers leading to marked catecholamine excess which can lead to hyperglycemia.[91]
- However, recent studies suggest that occurrence of pancreatitis may be responsible as hyperamylasemia often accompanies hyperglycemia. Though severe acute pancreatitis is not common, sub clinical pancreatic damage can occur following OP poisoning as shown by Dressel et al in canine experiments. In the experimental study they showed that OPCs cause an increase in intraductal pressure and exocrine pancreas flow rate which

results in extravasation of fluids.[92] While another study done in 2017 by Saleme et al showed that Serum Amylase levels may be considered as marker of Organophosphorus intoxication, since it enables the early recognition of those at risk of developing the complications of Organophosphorus poisoning.[110]

- Nicotinic receptors release excess of pituitary hormones. Persistent cholinergic stimulation could be causing changes in these hormones and can contribute to hyperglycaemia.
- There is also experimental evidence to suggest that hyperglycaemia could be as a result of increased breakdown of hepatic glycogen.[93]

METHODOLOGY

SOURCE OF DATA:

Patients who are admitted in BLDEDU'S Shri B.M.Patil's medical college hospital and research centre, Vijayapura with history of Acute Organophosphorus Poisoning after considering Inclusion and Exclusion criteria.

Period of study is from October 2018 to June 2020.

METHOD OF COLLECTION OF DATA:

Inclusion criteria

1. Patients or the relatives who have given informed written consent.
2. Patients who are above 18 years of age.
3. Patient with alleged history of organophosphorous poisoning (ingestion / inhalational / contact) and diagnosed to have organophosphorous poisoning.

Exclusion Criteria

1. Patients with history of Diabetes Mellitus.
2. Patients already treated at other centres and referred to our centre for further management with no details available at the time of first presentation.
3. Patients who had consumed alcohol, drugs, mixed poisoning that could affect the glycemic status of the patients.

STUDY DESIGN:

Cross sectional observational study

A provisional diagnosis of OP poisoning was made on the basis of definite history of OP poisoning by the patient or attendants, and this was substantiated by examination of the container when available. The diagnosis was further substantiated by typical clinical features (miosis, hypersalivation, fasciculation) and characteristic odour of stomach wash or vomitus.

Each patient enrolled for study underwent a detailed clinical examination as per the proforma, specially designed for the study, which included examination for presence of respiratory failure, detailed assessment of CNS and cardiovascular examination.

All patients were given stomach wash, body and eye wash, in patients who had exposure via uncovered skin and / or eyes. This was followed by 1 gm bolus dose of PAM (Pralidoxime) by slow IV injection. Thereafter, a bolus dose of atropine (2 mg iv push) was administered after correcting cyanosis, till signs of atropinisation (clear lungs, dry axilla, dry mucosa, heart rate ≥ 100 bpm, and dilated pupils). All patients were monitored closely and continuously and all clinical signs assessed 12^{th} hourly till complete recovery and were followed till discharge from hospital.

Ventilator support was provided if patient had persistent cyanosis, hypoventilation, apnoea, persistent tachypnoea or deranged ABG (PaO_2 < 60 mm Hg, $PaCO_2$> 50 mm Hg, pH < 7.2)

Investigations:

All patients underwent following biochemical investigations whenever necessary -

a. Blood routine, Hb%, TC, DC, ESR
b. Urine Examination – Albumin, Glucose, Microscopy
c. Admission Blood glucose values
d. E.C.G
e. ABG
f. S. pseudocholinesterase.
g. Blood Urea/ Se Creatinine.
h. Se Electrolytes
i. Liver function tests

Method of Estimation of Serum Pseudocholinesterase

S-butyryl thiocholine iodide is used to estimate pseudocholinesterase .Dibucaine as inhibitor. Normal values of serum pseudocholinesterase are 4150 to 7200 U/L.

Statistical Analysis

- The data obtained were entered in a Microsoft Excel sheet, and statistical analysis was performed using statistical package for the social sciences (Verson 20).
- Results were presented as Mean (Median) ±SD, counts and percentages and diagrams.
- Association of Categorical variables was found using Chi square test. $p<0.05$ will be considered statistically significant. All statistical tests will be Performed two tailed.

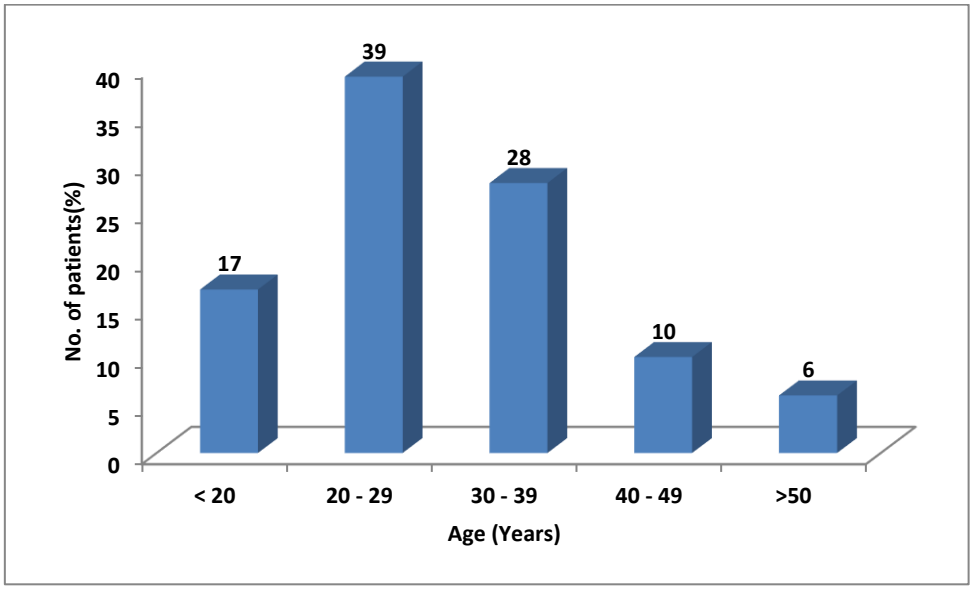
RESULTS

100 patients of OPC poisoning were studied resulting in-

Table 05: Distribution of patients according to Age (Years)

Age(Years)	No. of patients	Percentage
< 20	17	17.0
20 - 29	39	39.0
30 - 39	28	28.0
40 - 49	10	10.0
50+	6	6.0
Total	100	100.0

- Age groups range from 18-65 years.
- Majority of the patients are found in the age group of 20-39 years. (67%).
- Mean age of the study population is 29.49 +/- 9.909 years.

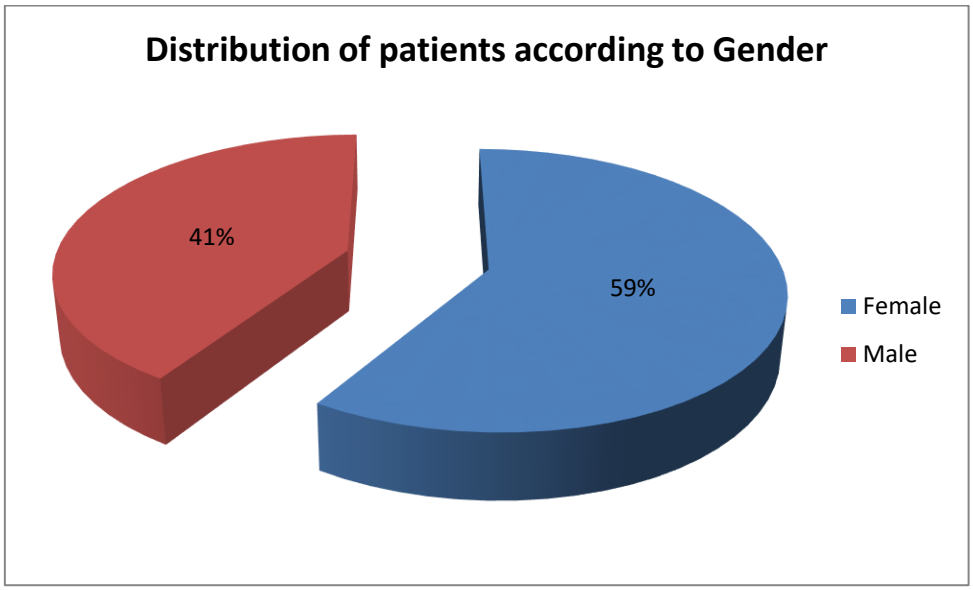


Graph 1: Distribution of patients according to age (yrs)

Table 06: Distribution of patients according to Gender

Gender	No. of patients	Percentage
Female	59	59.0
Male	41	41.0
Total	100	100.0

- Out of 100 patients, 59 were females and 41 were males with female to male ratio of 1.43:1
- In this study female predominance is seen 59%.

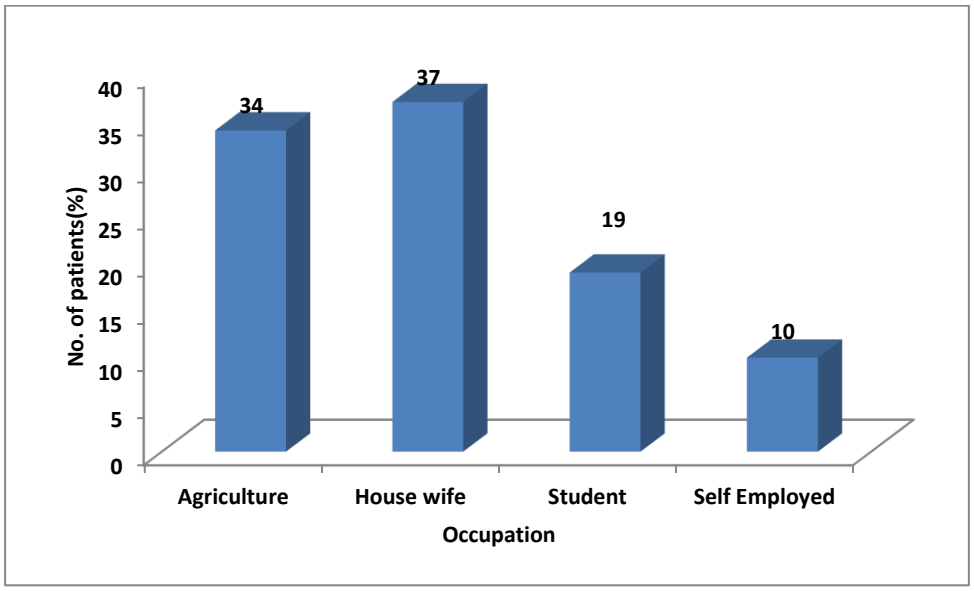


Graph2: Distribution of patients according to gender.

Table 07: Distribution of patients according to Occupation

Occupation	No. of patients	Percentage
Agriculture	34	34.0
House wife	37	37.0
Student	19	19.0
Self Employed	10	10.0
Total	100	100.0

- Housewives are the main group (37%) followed by agricultural workers (34%).

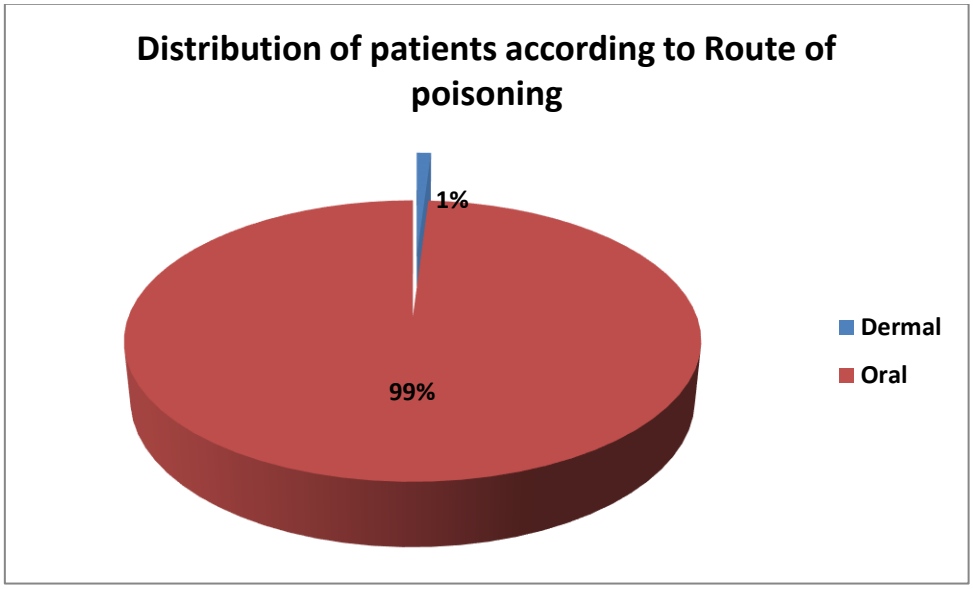


Graph 3: Distribution of patients according to occupation

Table8: Distribution of patients according to Route of poisoning

Route	No. of patients	Percentage
Dermal	1	1.0
Oral	99	99.0
Total	100	100.0

- Ingestion in 99 cases was the main route of poisoning.
- No cases were reported with inhalational route of poisoning



Graph 4: Distribution of patients according to route of poisoning

Table9: Distribution of patients according to Motive of poisoning.

Motive	No. of patients	Percentage
Accidental	1	1.0
Suicidal	99	99.0
Total	100	100.0

- 99 cases were due to suicide and 1 was accidental in nature.
- So suicidal ingestion was the main motive of poisoning.

Graph 5: Distribution of patients according to motive of poisoning

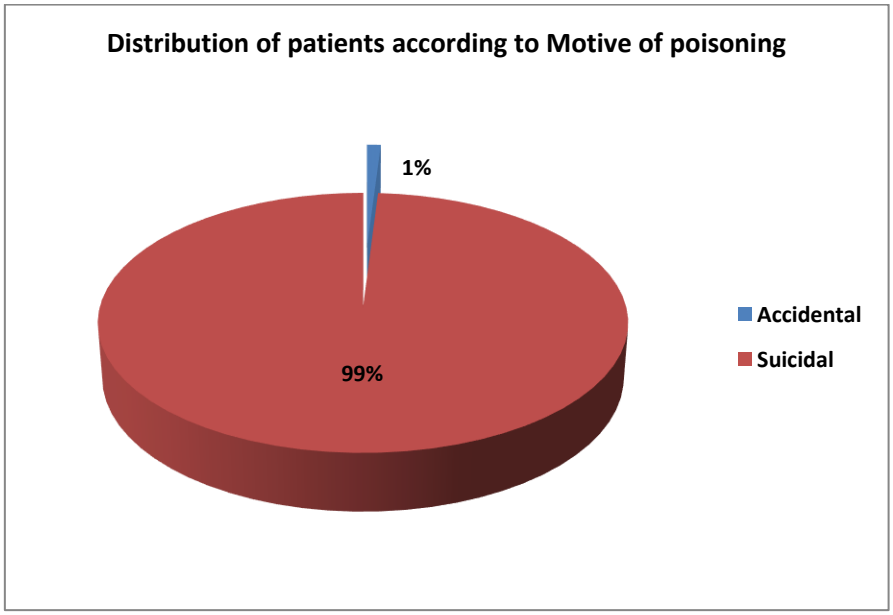
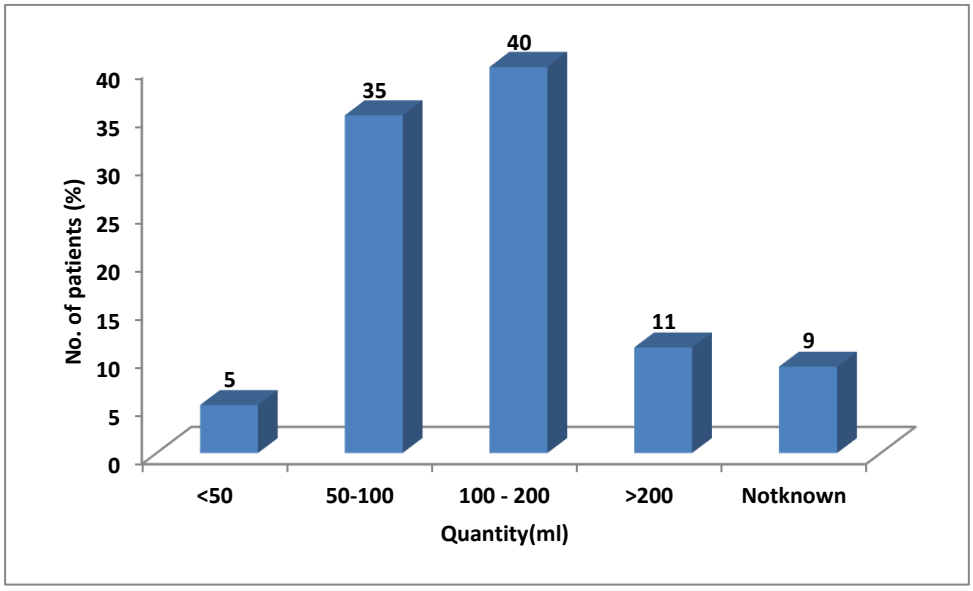


Table 10: Distribution of patients according to Quantity of consumption

Quantity (ml)	No. of patients	Percentage
<50	5	5.0
50-100	35	35.0
100 - 200	40	40.0
>200	11	11.0
Not known	9	9.0
Total	100	100.0

- In this study, majority of the patients had consumed 100-200ml of OP compound. (40%).

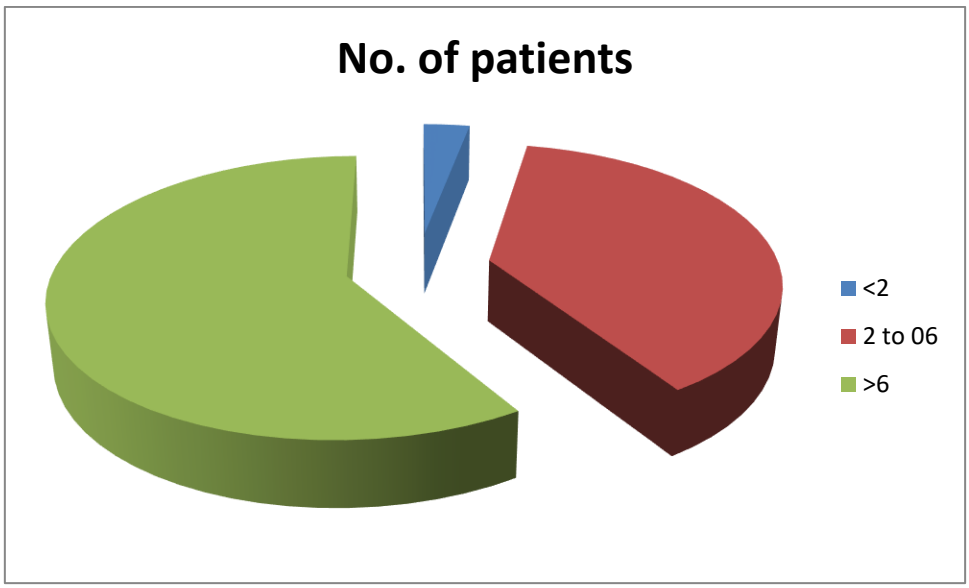


Graph 6: Distribution of patients according to quantity of consumption

Table 11: Distribution of patients according to Time Interval between consumption of OP compound and hospitalisation

Time Interval (Hours)	No. of patients	Percentage
<2	3	3.0
2-6	38	38.0
>6	59	59.0
Total	100	100.0

In this study, majority of patients (59%) were brought to hospital after 6 hours of exposure to the poison.

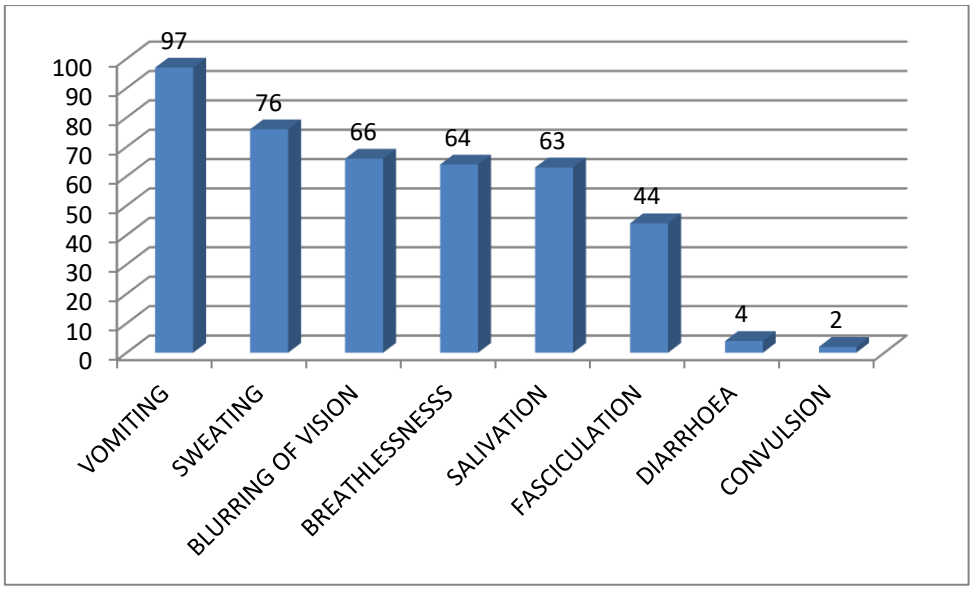


Graph 7: Distribution of patients according to Time Interval

Table 12: Distribution of patients according to Symptoms

Symptoms	No. of patients	Percentage
Vomiting	97	97.0
Sweating	76	76.0
Blurring	66	66.0
Breathlessness	64	64.0
Salivation	63	63.0
Fasciculation	44	44.0
Diarrhoea	4	4.0
Convulsion	2	2.0

- In this study, majority of the patients (97%) presented with symptom of vomiting, followed by sweating (76%), blurring of vision (66%).

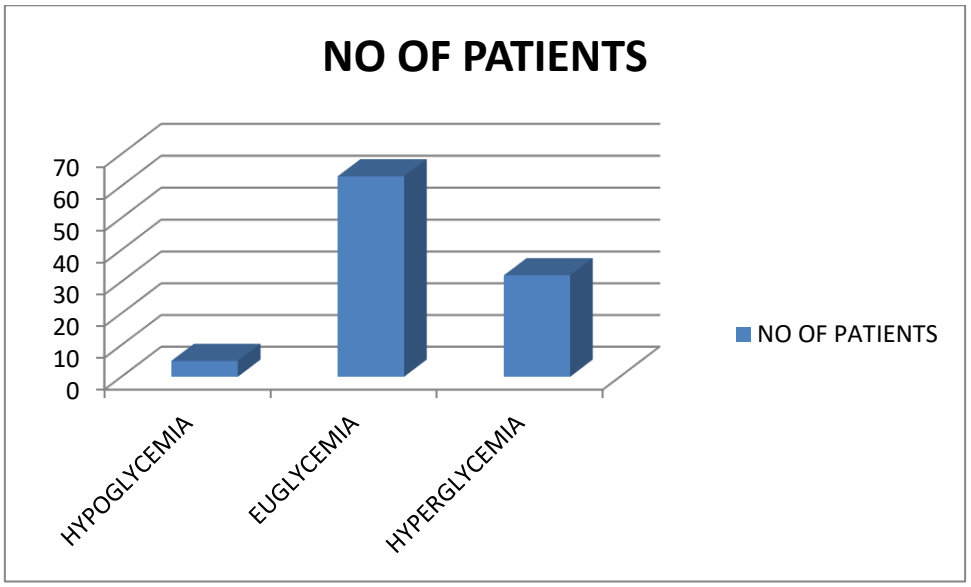


Graph 8: Distribution of patients according to symptoms

Table 13: Distribution of patients according to RBS at time of Admission

RBS	No of patients	Percentage
Hypoglycaemic	05	05
Euglycemic	63	63
Hyperglycemic	32	32

- In this study, 32 patients were found to be hyperglycaemic.

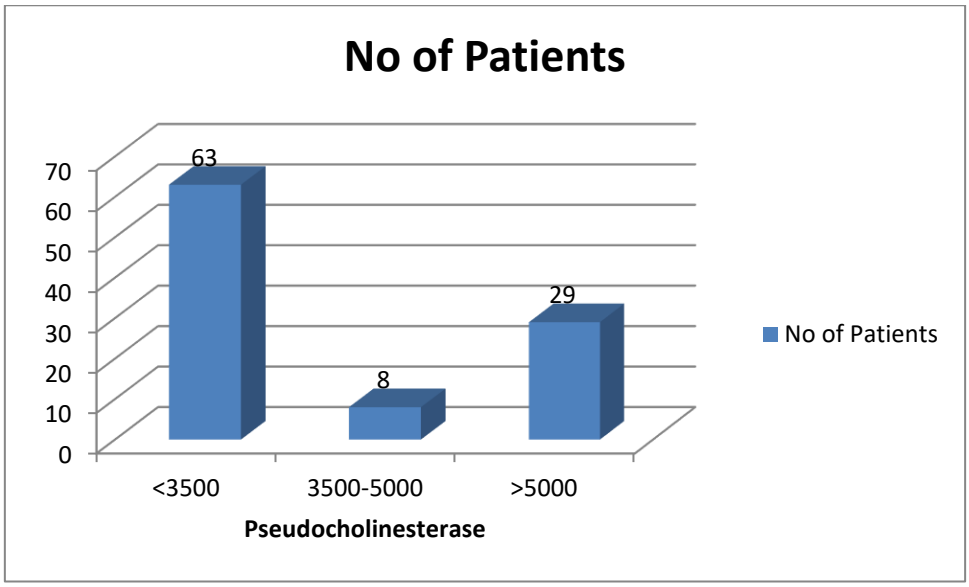


Graph 9: Distribution of patients according to RBS at time of admission

Table 14: Distribution of patients according to Admission Pseudocholinesterase levels

Pseudocholinesterase	No of Patients	Percentage
<3500	63	63
3500-5000	08	08
>5000	29	29

- 71 out of 100 patients included in the study had decreased Pseudocholinesterase levels.

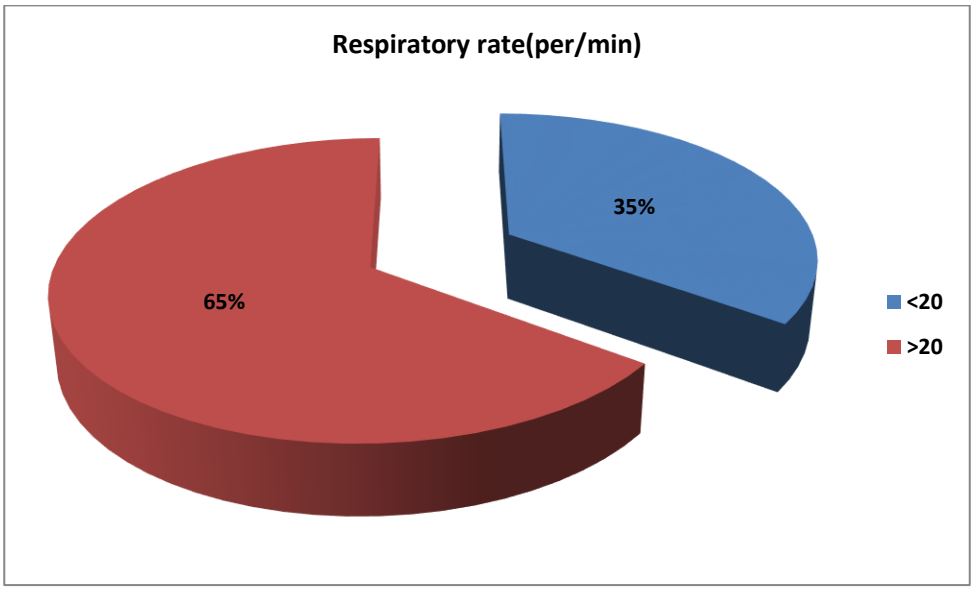


Graph10: Distribution of patients according to Admission Pseudocholinesterase levels

Table 15: Distribution of patients according to Respiratory rate

Respiratory rate (Per/min))	No. of patients	Percentage
<20	35	35.0
>20	65	65.0
Total	100	100.0

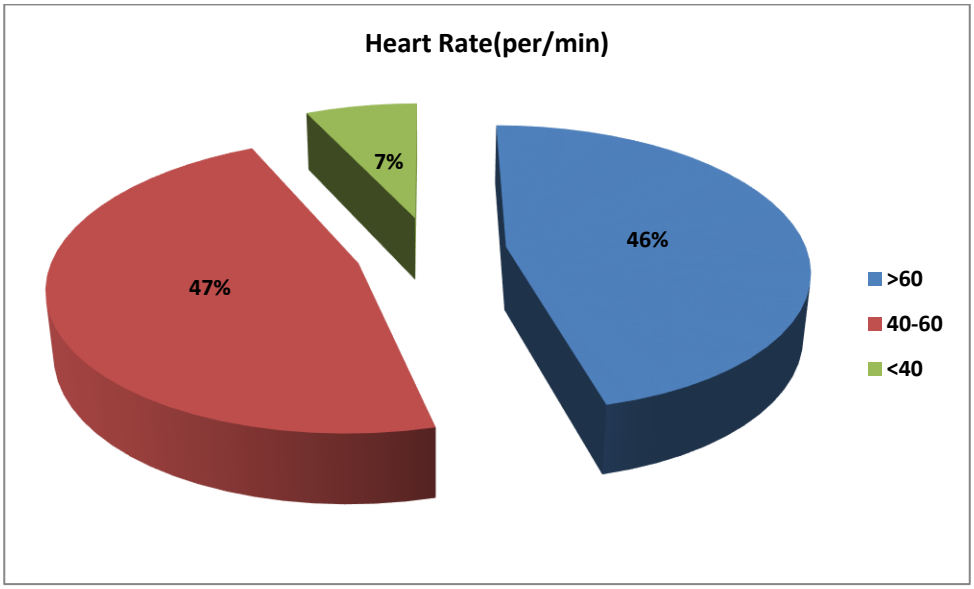
- In our study, 65% patients were found to have respiratory rate above 20cpm.



Graph 11: Distribution of patients according to Respiratory rate

Table 16: Distribution of patients according to Heart rate

Heart rate (Per/min))	No. of patients	Percentage
>60	46	46.0
40-60	47	47.0
<40	7	7.0
Total	100	100.0

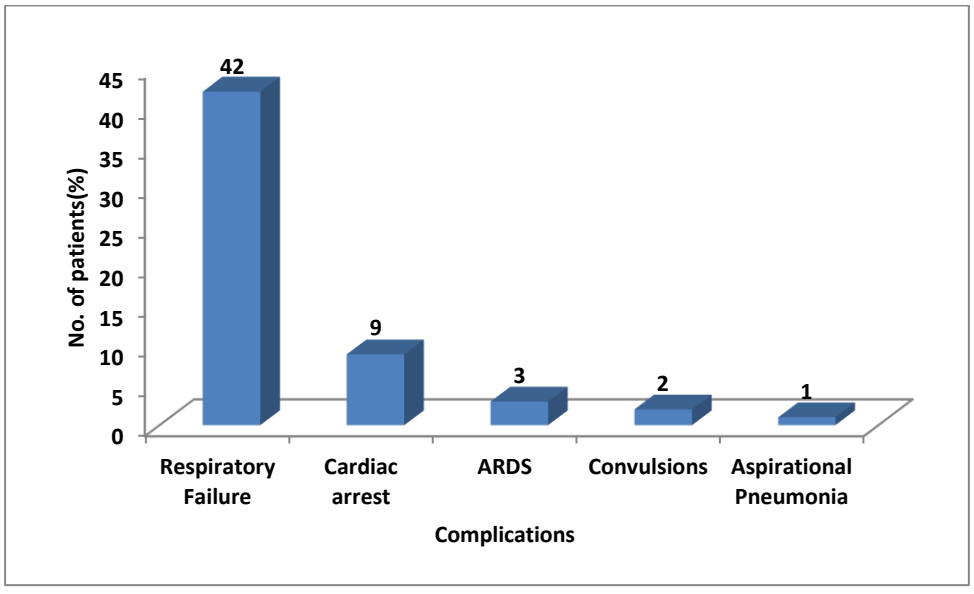


Graph 12: Distribution of patients according to Heart rate

Table 17: Distribution of patients according to Complications

Complications	No. of patients	Percentage
Respiratory Failure	42	42.0
Cardiac arrest	09	9.0
ARDS	03	3.0
Convulsions	02	2.0
Aspirational Pneumonia	01	1.0

- In this study, 42% patients were found to have at least one complication during the course of hospitalisation.
- Respiratory failure was found in all patients developing complication, out of which 25 of them needed ventilator support.

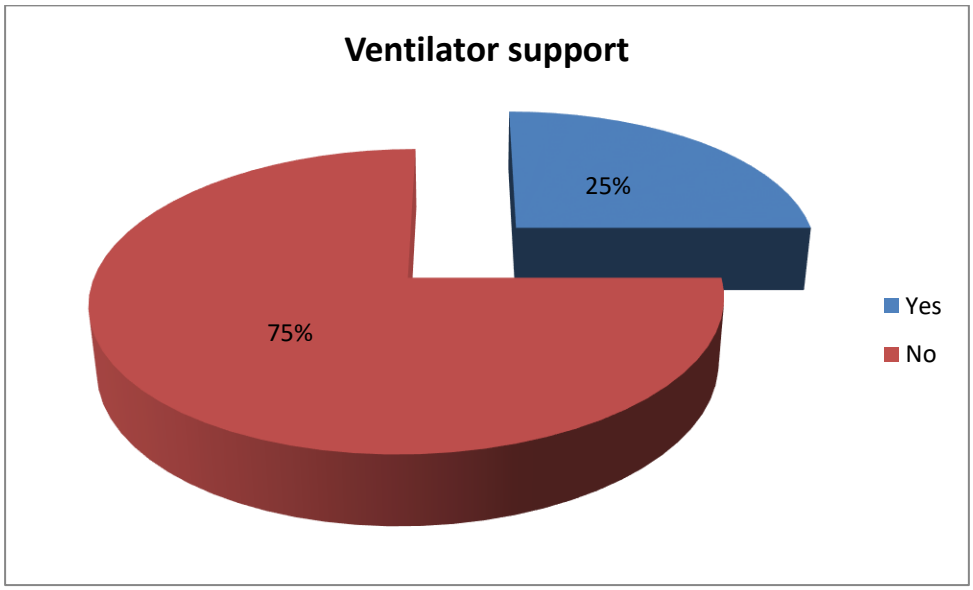


Graph 13: Distribution of patients according to Complications

Table 18: Distribution of patients according to Ventilator support

Ventilator support	No. of patients	Percentage
Yes	25	25.0
No	75	75.0
Total	100	100.0

- In this study, 25% of the patients needed ventilator support.



Graph 14: Distribution of patients according to Ventilator support

Table 19: Association between RBS and Complications

RBS	Complications			Chi square test	P value
	No	Yes	Total		
Hypoglycaemia	1	4	5	X^2=23.246	P=0.001*
%	1.7%	9.5%	5.0%		
Normoglycemia	48	15	63		
%	82.8%	35.7%	63.0%		
Hyperglycemia	9	23	32		
%	15.5%	54.8%	32.0%		
Total	58	42	100		
*:Highly significant					

- At least one complication were found in 42 patients out of 100 included in the study, out which 23 patients presented with hyperglycaemia, 4 with hypoglycaemia and 15 with normoglycemia.
- Of all the patients presented with hyperglycemia (32), 23 of the patients developed at least one complication, while only 15 out of 63 patients who presented with normoglycemia developed complications.

Graph 15: Association between RBS and Complications

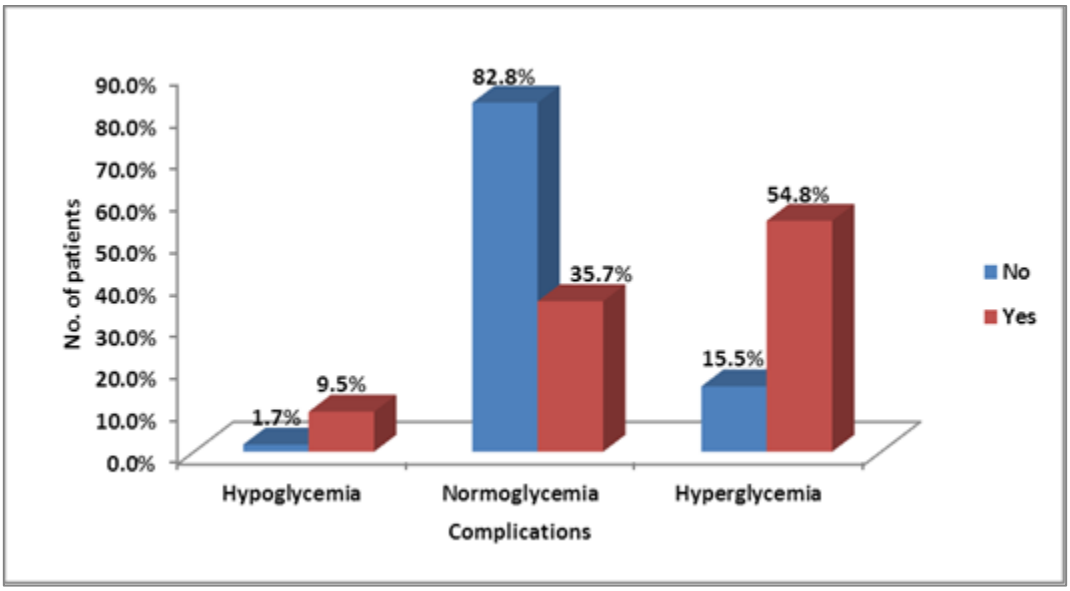
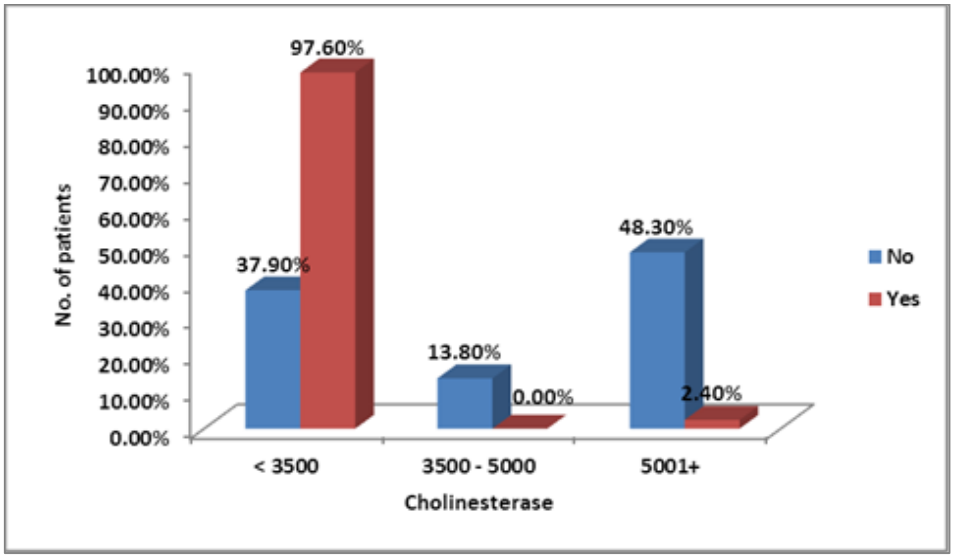


Table 20: Association between Cholinesterase and Complications

Cholinesterase	Complications			Chi square test	P value
	No	Yes	Total		
< 3500	22	41	63	X^2=37.262	P=0.001*
	37.9%	97.6%	63.0%		
3500 - 5000	8	0	8		
	13.8%	0.0%	8.0%		
5001+	28	1	29		
	48.3%	2.4%	29.0%		
Total	58	42	100		
*:Highly significant					

- In this study, complications were more prevalent with reduced pseudocholinesterase levels.

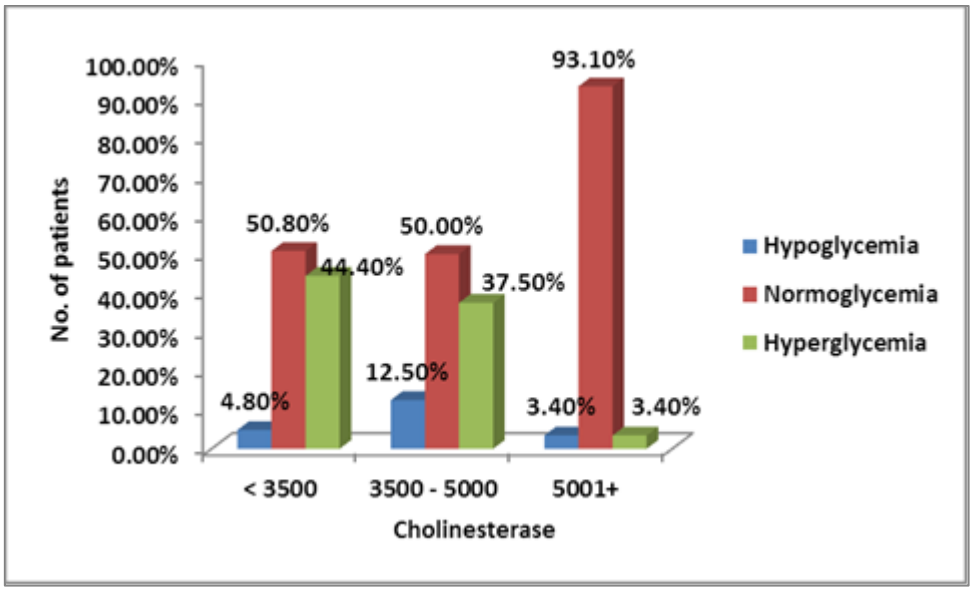


Graph 16: Association between Cholinesterase and Complications

Table 21: Association between RBS and Cholinesterase

RBS	Cholinesterase				Chi square test	P value
	< 3500	3500 - 5000	5001+	Total		
Hypoglycaemia	3	1	1	5	X^2=17.435	P=0.004*
%	4.8%	12.5%	3.4%	5.0%		
Normoglycemia	32	4	27	63		
%	50.8%	50.0%	93.1%	63.0%		
Hyperglycemia	28	3	1	32		
%	44.4%	37.5%	3.4%	32.0%		
Total	63	8	29	100		
*:Highly significant						

- In this study, 28 out of 32 patients who presented with hyperglycemia had reduced pseudocholinesterase which was highly significant.

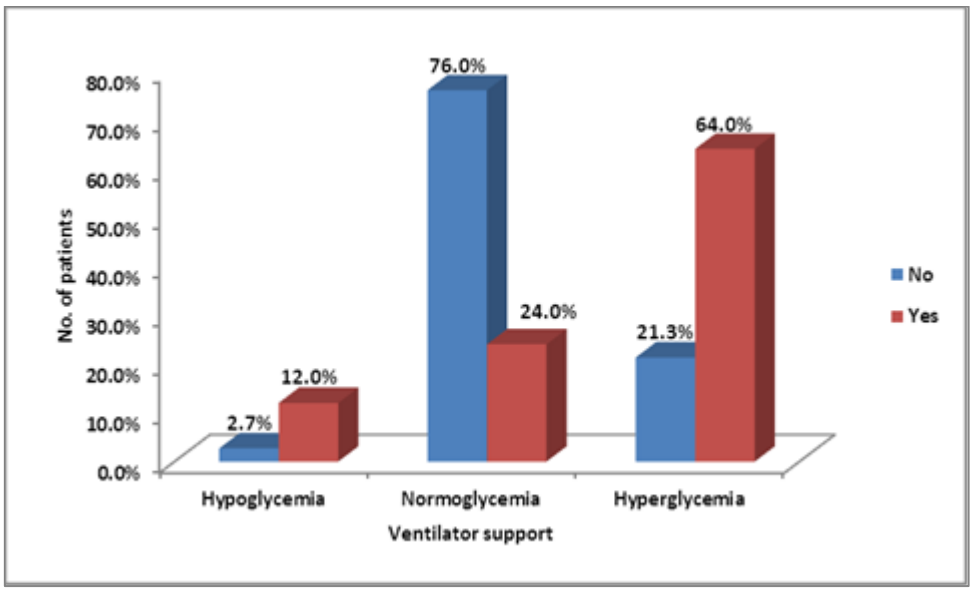


Graph 17: Association between RBS and Cholinesterase

Table 22: Association between RBS and Ventilator support

RBS	Ventilator support			Chi square test	P value
	No	Yes	Total		
Hypoglycaemia	2	3	5	X^2=21.981	P=0.001*
%	2.7%	12.0%	5.0%		
Normoglycemia	57	6	63		
%	76.0%	24.0%	63.0%		
Hyperglycemia	16	16	32		
%	21.3%	64.0%	32.0%		
Total	75	25	100		
*:Highly significant					

- In this study, out of 32 patients who presented with hyperglycemia, 16 of them needed ventilator support.

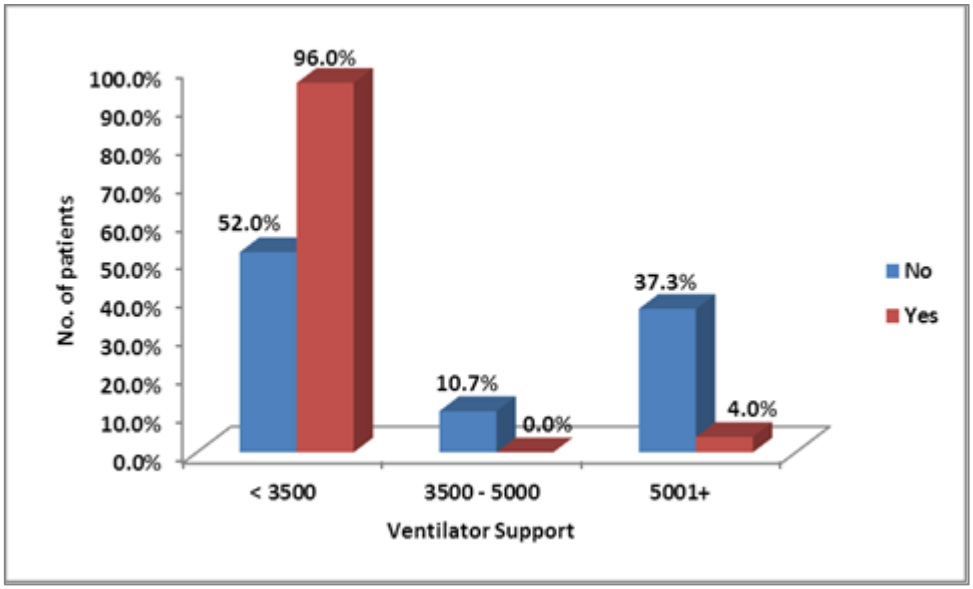


Graph 18: Association between RBS and ventilator support

Table 23: Association between Cholinesterase and Ventilator Support

Cholinesterase	Ventilator support			Chi square test	P value
	No	Yes	Total		
< 3500	39	24	63	X^2=15.612	P=0.001*
	52.0%	96.0%	63.0%		
3500 - 5000	8	0	8		
	10.7%	0.0%	8.0%		
5001+	28	1	29		
	37.3%	4.0%	29.0%		
Total	75	25	100		
*:Highly significant					

- In this study, out of 25 patients who needed ventilator support, 24 of them had reduced pseudocholinesterase levels.

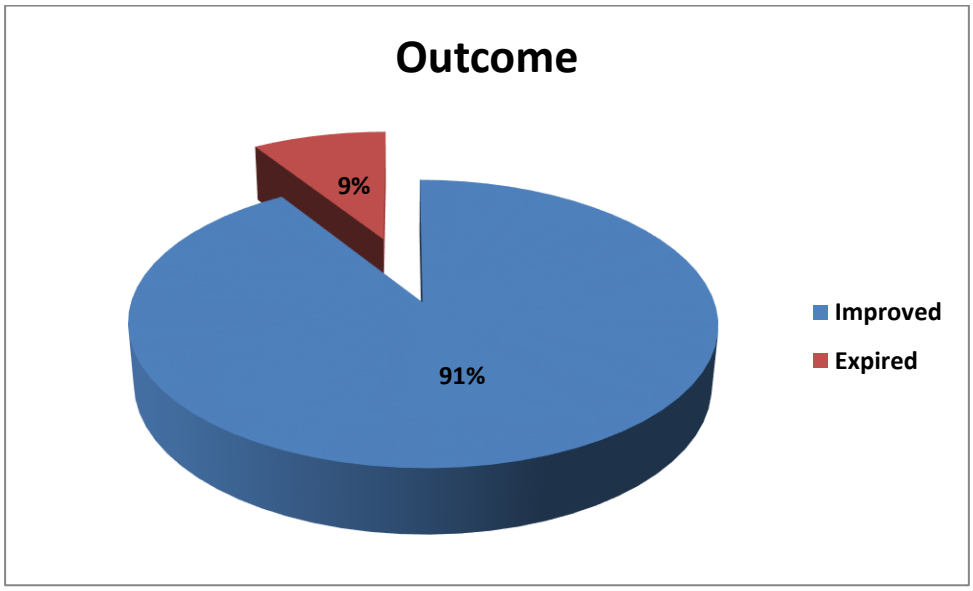


Graph 19: Association between Cholinesterase and Ventilator Support

Table 24: Distribution of patients according to Outcome

Outcome	No. of patients	Percentage
Improved	91	91.0
Expired	9	9.0
Total	100	100.0

- In this study, out of 100 patients, 91 of them recovered, while nine of them expired due to complications.
- Out of the 9 patients who expired, 5 patients presented with hyperglycaemia, 2 with hypoglycaemia and 2 with normoglycemia.



Graph 20: Distribution of patients according to Outcome

DISCUSSION

Acute Organophosphorus poisoning (OP) is widespread in the developing world and its frequency is increasing.[1] WHO has estimated that nearly 2 lakh people die from pesticide poisoning.

All OP patients cannot be treated in the intensive care unit. Thus it is important that clinical features and other factors which indicate severity of poisoning, the need for ventilator support are assessed in causality only. In a study done by Gunduz et al in 2015 showed that Bradycardia, Age , Blood Glucose levels, Lactate Dehydrogenase and Acidosis are independent predictors of mortality in patients with Organophosphorus Poisoning.[114]

Table 25: STUDIES COMPARING AGE GROUP

Age group	Present study (%)	Shankar PS et al[95] (%)	Lograj M et al[94] (%)
< 20	17	25	65.85
20 – 29	39	59.4	
30 – 39	28	9.4	21.54
40 – 49	10	6.2	6.85
50+	6	-	5.76

- In this study, maximum incidence of poisoning was among 20-29 years of age group (39%) which is consistent with the studies done by Shankar PS et al[95] and Lograj M et al[94].
- Mean age of the study population is 29.49 +/- 9.909 years which is comparable with observations in studies done by Mohammad Mir et al[118], Panda s et al[108] and Raghapriya et al[119].

Table 26: STUDIES COMPARING GENDER

Gender	Present study (%)	Goel et al[98] (%)	Vikram P et al[96] (%)	Shobha TR et al[97] (%)	Karki P et al[101] (%)	Panda S et al[108] (%)
Male	41	72	75.1	56.6	46	40
Female	59	28	24.9	33.4	54	60

- Female were the more common victims in the present study in contrast to male predominance in findings of Goel et al[98,] Vikram P et al[96,] Shobha TR t al[97]but consistent with findings by Karki P et al[101] and Panda S et al.
- This could be attributed to the regional variations and the socioeconomic settings of various studies.

Table 27: STUDIES COMPARING MOTIVE OF POISONING

Motive	Present study (%)	Goel et al[98] (%)	Bhattarai et al[99] (%)	Vikram P et al[96] (%)
Suicidal	99	96.1	87.2	98.7
Accidental	01	3.9	12.8	1.3

- In the present study, majority of the cases motive were suicidal which was consistent with observations made by Vikram P et al[96], Goel etal[98], Bhattarai et al[99].
- Suicidal poisoning is very common since these compounds are easily available for everyone.

Table 28: STUDIES COMPARING MODE OF POISONING

Mode	Present study (%)	Sungur M et al[100] (%)
Ingestion	99	93.6

Ingestion was the most common mode used for self poisoning by the patients which is comparable to the findings by Sungur M et all[100].

Table 29: STUDIES COMPARING CLINICAL FEATURES

CLINICAL FEATURES	PRESENT STUDY (%)	Adlakha et al[102] (%)	Singh S et al[103] (%)	Goel et al[98] (%)	Panda S et al[108] (%)
Vomiting	97	56	90	97.08	82
Hyper salivation	63	36	80	28.15	71
Seizures	2	11	20	-	-

- Vomiting was the commonest symptom in 94% followed by sweating and hyper salivation which are comparable to studies done by Adlakha et al[102], Singh S et al[103], Goel et al[98] , Panda S et al[108].

Table 30: STUDIES COMPARING COMPLICATIONS

COMPLICATIONS	Present study	Goel et al[98]	Sungur M et al[100]
Respiratory Failure	42	34.95	29.7
ARDS	3	2.3	-
Pneumonia	1	-	-

- Respiratory Failure was the most common complication seen in 42% which is comparable to Goel et al[98], Sungur M et al[100]studies.

Table 31: STUDIES COMPARING HYPERGLYCEMIA

STUDY	HYPERGLYCEMIA
Present study	**32**
Sungur M et al[100]	**31.9**
Shobha et al[97]	**26**
Ravindra K.R et al[106]	**20**

- Hyperglycemia was detected in 32% of the patients in this study which is comparable to findings in the study by Sungur M et al[100], Shobha et al[97,] Ravindra K.R et al[106].
- In this study it was observed that on complications associated with on admission hyperglycemia (RBS>160 mg/dl) was 54.8% as compared to 35.7% in normoglycemics. This is highly significant (p=0.001).

- In addition hyperglycemia also showed a significant association with need for ventilator support (p=0.001).64% of patients with hyperglycemia were found to need ventilator support as compared to 24% with normoglycemia.

Table 32: STUDIES COMPARING PSEUDOCHOLINESTERASE LEVELS

Pseudocholinesterase (IU/L)	Present Study (%)	Rao R et al[107] (%)
Normal	29	26
Moderate Depression	25	42
Severe Depression (<1000)	46	32

- In our study, 61% had reduction of Pseudocholinesterase levels with 46 of them having severe depression which is comparable to Rao R et al[107].
- The mean Pseudocholinesterase levels were 2701.23 IU/L which is comparable to findings by Jeong Mi Moon et al[109] (2736.0 IU/L)
- In our study it was noted that Pseudocholinesterase values<3500U/L (p=0.001) was associated with complication in 97.6% of the cases and ventilator support in 96 %(p<0.001), these observations were statistically significant.
- The present study showed an overall mortality of 9 % comparable with BardinPG et al[104], Singh S et al[105], Sert et al[115].

- Mortality rate of 28% was observed in patients with hyperglycemia which was highly significant ($p<0.05$).
- The above results indicate RBS value >160mg/dl is a good marker for predicting the mortality and also for assessing the need for ventilator support.
- Admission RBS was comparable to the drop in pseudocholinesterase levels, with a $p=0.004$ which was highly significant.
- These observations suggest that admission hyperglycemia is a prognostic indicator in OP compound poisoning and it is comparable to pseudocholinesterase. Further studies are needed in this area.
- Out of 9 patients who expired, 5 patients had hyperglycaemia at presentation with 3 of them having RBS > 200 mg/dl.
- Hyperglycaemia is directly proportional and serum Pseudocholinesterase is inversely proportional to the in-hospital complications, ventilator support and mortality of patients with OP poisoning.

CONCLUSION

- Organophosphorus Compound poisoning is more commonly seen in young males and Housewives of Agricultural background.
- Poisoning is diagnosed on the basis of history and clinical examination which can be confirmed by biochemical investigation.
- Hyperglycemia can occur in moderate to severe organophosphorous poisoning.
- The occurrence of hyperglycemia correlates with complications, requirement of ventilator support and poor prognosis.
- Hyperglycemia is also correlated with low levels of pseudocholinesterase in predicting mortality and ventilator support.
- More the Blood Glucose levels at the time of presentation, more is the complication, ventilator support and mortality.
- In conclusion admission RBS >160 mg/dl can be considered as a prognostic factor in predicting the morbidity and mortality of organophosphorous poisoning.

SUMMARY

- 100 cases of OP poisoning admitted to BLDEDU's Shri B M Patil Medical College Hospital from October 2018 – June 2020 were included in the study.
- Most common age group involved is between 20-39 years.
- Females, commonly Housewives are the most common victims followed by Agricultural workers.
- Suicide was the most common motive of poisoning (99%) and ingestion was the most common mode of poisoning (99%).
- Majority of patients admitted after 6 hours of exposure.
- Vomiting, (97%), Sweating (76%), Hyper salivation (63%) are the most common symptoms.
- Respiratory failure was the most common complication (42%).
- Hyperglycemias occurred in 32% of patients with 54.8% developing complications and 64% requiring ventilator.
- Pseudocholinesterase was less than 3500U/L in 63% of patients with complications occurring in 68% of them and 49% requiring ventilator support.
- Overall mortality was 9%.

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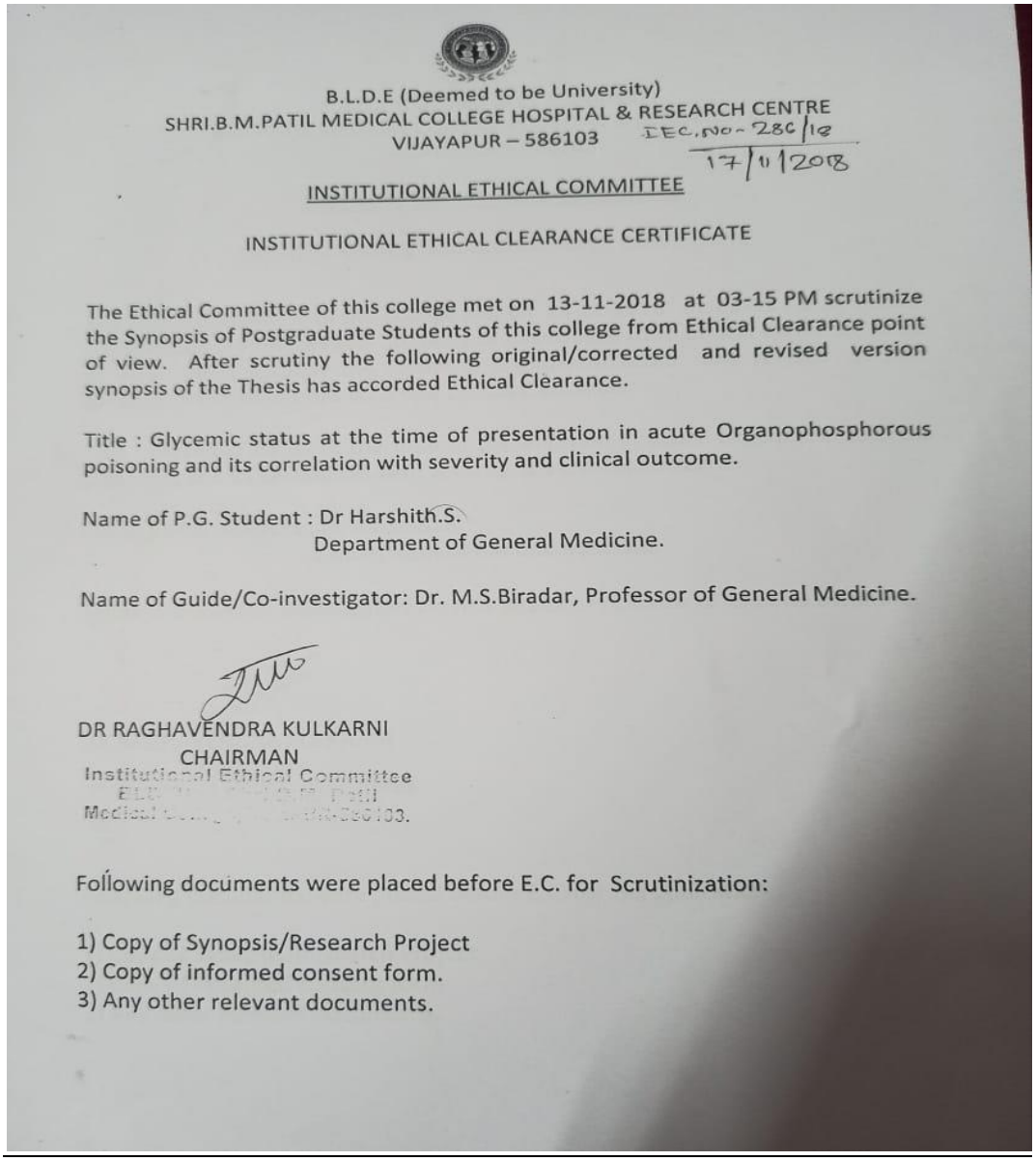
ANNEXURE – 1

ETHICAL COMITTEE CLEARANCE CERTIFICATE



B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC.No-280/18
17/11/2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : Glycemic status at the time of presentation in acute Organophosphorous poisoning and its correlation with severity and clinical outcome.

Name of P.G. Student : Dr Harshith.S.
Department of General Medicine.

Name of Guide/Co-investigator: Dr. M.S.Biradar, Professor of General Medicine.

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
B.L.D.E (Deemed to be University)
Shri.B.M.Patil
Medical College Hospital & Research Centre
Vijayapur-586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

ANNEXURE –II

INFORMED CONSENT FORM

BLDEU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA- 586103

TITLE OF THE PROJECT- **Glycemic Status at the Time of Presentation in Acute Organophosphorous Poisoning and its Correlation with Severity and Clinical Outcome**

PRINCIPAL INVESTIGATOR - **Dr HARSHITH S**

P.G.GUIDE NAME - **Dr. M S BIRADAR**
MD (GENERAL MEDICINE)
VICE CHANCELLOR AND PROF
OF MEDICINE BLDE UNIVERSITY

CHAIRMAN ETHICAL COMMITTEE

All aspects of this consent form are explained to the patient in the language understood by him/her.

1) PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary

investigations and treatment, which will help the investigator in this study.

3) RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

4) BENEFITS:

I understand that my participation in this study will help to patients survival and better outcome.

5) CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. HARSHITH S is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the

study, which might influence my continued participation.

If during the study, or later,I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. HARSHITH S may terminate my participation in the study after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate.

8) INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Dr.HARSHITH S Date:

(Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr. HARSHITH S**has explained to me the purpose of research, the study procedures 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

PROFORMA

Study- Glycemic Status at the Time of Presentation in Acute Organophosphorous Poisoning and its Correlation with Severity and Clinical Outcome

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Past Occupation:

Present Occupation:

Residence:

Chief complaints:

History of present illness:

Past History:

History of diabetes mellitus

History of hypertension

History of IHD

History of tuberculosis

History of Hepatic or Renal diseases

Personal History:

Diet/appetite:

Sleep

Bladder and bowel habits :

Smoking/Tobacco chewing/Drug Intake-Snuff Inhalation/alcohol:

Family History:

PTB: Br.Asthma: Malignancy: DM: HTN:

Treatment History

General Physical Examination

Consciousness :

Orientation:

Height :

Weight:

Body Mass Index :

Vitals

Pulse rate:

Blood pressure:

Respiratory rate:

Temp:

Head to toe examination:

Pupils:

Secretions:

Fasciculations:

SYSTEMIC EXAMINATION.

Respiratory System

Cardiovascular System

Central Nervous System

Per abdomen

INVESTIGATIONS

1. HAEMATOLOGY –

Haemoglobin	gm %
Total WBC counts	Cells/mm^3
Differential counts -	
N- % , L - % , Eo - %	Mo - % , Ba - %
ESR	mm after 1 hour

2. URINE EXAMINATION -

Albumin	
Sugar	
Microscopy	

3. Random blood glucose level at the time of admission.
4. ECG
5. Pseudocholinesterase levels at the time of admission.
6. Serum creatinine and blood urea.
7. Liver function tests.
8. HbA1C (if hyperglycemia documented)
9. Stomach Wash Analysis

CHEST X RAY:

PERADENIYA SCALING SYSTEM :

Parameter	Criteria	Score
Pupil size	≥2 mm	0
	<2 mm	1
	pinpoint	2
Respiratory rate	<20/min	0
	≥20/min	1
	≥20/min with central cyanosis	2
Heart rate	>60/min	0
	41-60/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 command	1
	No response to verbal command	2
Seizures	Absent	0
	present	1

FINAL DIAGNOSIS

TREATMENT GIVEN

COMPLICATIONS

OUTCOME:

KEY TO MASTER CHART

Sl. No.-Serial number

I.P No-In patient number

F-Female

M-Male

HW-House wife

S-Student

A-Agriculture

PE-Private employee

SE- Self employee

S-Suicidal

A-Accidental

O-Oral

I-Inhalational

D-Dermal

Quantity:

A: 51-100 ML

B- 101-150 ML

C- 151-200ML

D:> 200 ml

N-Not Known

Time interval:

A:< 2 hrs , B:2 - 6 hrs , C:> 6 hrs

Clinical features

Y-Yes, N- No

Respiratory Rate

A-20/mt

B-> 20/mt

C-< 20/mt with Cyanosis

Pulse Rate

A->60/mt

B-40 - 60/mt

C-< 40/mt

Type of complication

C-Convulsion

I-Intermediate syndrome

A-ARDS

AP-Pneumonia

RF-Respiratory Failure

CA-Cardiac Arrest

Outcome & follow up

I-Improved

D-Expired

MASTER CHART

SL NO	NAME	IP NO	AGE	SEX	OCCUPATION	DURATION	ROUTE	INTENTION	QUANTITY	TIME INTERVAL	VOMITING	SALIVATION	SWEATING	LACRIMATION	BLURRING	BREATHLESS	BOWEL	CONVULSION	FASCICULATION	RR	HR	COMPLICATION		VENTILATOR	RBS	CHOLINESTERASE	OUTCOME
1	SANGAMESHWAR	30546/18	40	M	A	10	O	S	D	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		Y	183	200	I
2	MAYAWWA	33225/18	35	F	HW	6	O	S	B	B	Y	Y	N	N	N	N	N	N	N	A	A			N	120	2750	I
3	LAGAMANNA	33524/18	55	M	A	7	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	A	RF		N	209	310	I
4	KASHIBAI	30826/18	50	F	HW	7	O	S	C	C	Y	Y	Y	Y	Y	Y	Y	N	N	A	A	RF		Y	165	310	I
5	MAHADEVI	35988/18	28	F	A	3	O	S	N	B	Y	N	N	N	N	N	N	N	N	A	A			N	106	8190	I
6	SHRUTI	36477/18	25	F	S	9	O	S	D	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		N	125	260	I
7	MUTTU	36416/18	30	M	A	6	O	S	D	C	Y	Y	Y	Y	Y	Y	N	Y	Y	B	C	RF, CA,	C,ARDS	Y	149	200	D
8	SANTOSH	37180/18	28	M	SE	7	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		N	131	200	I
9	BASAVARAJ	36308/18	38	M	A	2	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	N	B	A	RF,ARDS,	CA	Y	55	6070	D
10	JANABAI	39160/18	32	F	HW	3	O	S	B	B	Y	N	N	N	N	N	N	N	N	A	A			N	92	6470	I
11	LAGAMAWWA	39168/18	45	F	A	5	O	S	N	C	Y	Y	Y	N	N	Y	N	N	N	B	B	RF		N	99	200	I
12	MAHADEV	39853/18	25	M	HW	7	O	S	N	B	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		N	61	200	I
13	MAHESH	38703/18	23	M	A	13	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		Y	161	200	I
14	PALLAVI	40021/18	25	F	HW	6	O	S	C	B	Y	Y	Y	N	Y	Y	N	N	N	A	B	RF		Y	210	1900	I
15	IRANNA	40128/18	29	M	A	7	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		N	113	200	I
16	MAHADEVI	40644/18	18	F	HW	14	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		Y	148	200	I
17	BUDDAPPA	39647/18	40	M	A	7	O	S	D	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	C	RF		Y	69	200	I
18	MALLIKARJUN	43619/18	32	M	SE	3	O	S	A	B	N	N	N	N	N	N	N	N	N	A	A			N	85	8800	I
19	SHRISHAIL	43436/18	18	M	SE	4	O	S	C	B	Y	Y	Y	B	Y	Y	N	N	N	B	A			N	84	1020	I
20	JYOTI	43029/18	22	F	HW	6	O	S	C	B	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		N	189	200	I
21	ANU	42974/18	20	F	HW	6	O	S	D	C	Y	Y	Y	Y	Y	Y	Y	N	Y	B	C	RF,CA		Y	193	200	D
22	RENUKA	41361/18	51	F	HW	20	O	S	C	B	Y	Y	Y	N	Y	N	N	N	N	B	B	RF		Y	116	400	I
23	RAVINA	1172/19	22	F	S	4	O	S	A	B	Y	N	N	N	N	N	N	N	N	A	A			N	85	6810	I
24	ASHWINI	915/19	19	F	S	8	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		N	173	200	I

25	GEETHABAI	2888/19	25	F	HW	5	O	S	N	B	N	N	N	N	N	N	N	N	N	A	A			N	104	7750	I
26	BISMILLA	2950/19	29	M	SE	5	O	S	B	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B			N	142	560	I
27	MANJULA	2100/19	30	F	HW	4	O	S	B	B	Y	N	Y	N	N	N	N	N	N	A	A			N	159	3590	I
28	KAREPPA	3524/19	38	M	A	7	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		Y	185	220	I
29	KAVERI	5552/19	18	F	HW	7	O	S	B	C	Y	Y	Y	N	Y	Y	N	N	N	B	A			N	154	3680	I
30	SOMANING	4311/19	30	M	A	5	D	A	N	B	N	N	Y	N	N	N	N	N	N	A	A			N	102	7880	I
31	SUSHMITHA	6097/19	26	F	HW	4	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		N	179	200	I
32	VIJAY	6730/19	25	M	SE	4	O	S	B	B	Y	N	Y	N	N	N	N	N	N	B	A			N	100	2020	I
33	SHANTHABAI	9086/19	45	F	A	6	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		N	120	200	I
34	SHIRIN	8670/19	23	F	SE	6	O	S	B	C	Y	Y	Y	N	Y	Y	N	N	N	B	B			N	176	840	I
35	NEELAMMA	9168/19	19	F	HW	9	O	S	C	B	Y	Y	Y	N	Y	Y	N	N	N	B	B			N	179	1320	I
36	SHOBA	8314/19	30	F	HW	4	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF	ARDS	Y	215	200	I
37	VINOD	8105/19	18	M	A	3	O	S	A	B	Y	N	N	N	N	N	N	N	N	A	A			N	85	6390	I
38	MALKANNA	7681/19	35	M	A	11	O	S	C	C	Y	Y	Y	N	Y	Y	Y	N	Y	B	B	RF		N	89	200	I
39	SHALAKKA	11591/19	35	F	A	8	O	S	N	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B			N	126	340	I
40	ROOPA	12369/19	19	F	S	7	O	S	C	B	Y	Y	Y	N	Y	Y	N	N	N	B	A			N	161	1460	I
41	SAVITRI	13471/19	25	F	HW	15	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		Y	111	200	I
42	SOMU	13117/19	38	M	A	3	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF, AP	CA	Y	106	3030	D
43	PANAMMA	14870/19	30	F	HW	10	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		N	148	200	I
44	PREMA	16592/19	18	F	HW	5	O	S	A	B	Y	N	N	N	N	N	N	N	N	A	A			N	94	6900	I
45	KAREPPA	16311/19	28	M	A	16	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		N	187	260	I
46	SANTOSH	15711/19	30	M	SE	24	O	S	B	C	Y	Y	Y	N	Y	Y	N	N	N	B	B			N	107	1630	I
47	ROOPA	20634/19	26	F	HW	4	O	S	B	B	Y	N	N	N	N	N	N	N	N	A	A			N	97	6341	I
48	REVANASIDDA	22679/19	36	M	A	7	O	S	B	C	Y	N	Y	N	Y	Y	N	N	N	B	A			N	124	4815	I
49	TANAJ	26462/19	18	M	S	3	O	S	B	C	Y	N	Y	N	N	N	N	N	N	A	A			N	94	4116	I
50	SHRISHAIL	25697/19	23	M	A	4	O	S	N	C	Y	N	Y	N	N	N	N	N	N	A	A			N	93	5339	I
51	SHANTA	17176/20	45	F	HW	9	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		N	82	861	I
52	SAVITA	16502/20	25	F	HW	8	O	S	D	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	C	RF,CA		Y	60	200	D
53	MAHADEV	16190/20	30	M	SE	2	O	S	B	B	Y	N	N	N	N	N	N	N	N	A	A			N	78	6138	I
54	MALAPPA	16138/20	60	M	A	8	O	S	D	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		Y	81	200	I
55	MAYAKKA	15624/20	23	F	A	6	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		Y	180	200	I
56	MUSKAAN	15390/20	15	F	S	3	O	S	N	B	Y	N	N	N	N	N	N	N	N	A	A			N	100	7914	I

57	LALASAB	14169/20	45	M	A	5	O	S	D	C	Y	Y	Y	Y	Y	Y	N	Y	Y	B	C	RF,C,CA		Y	115	200	D
58	MAHADEVI	14055/20	23	F	HW	4	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	N	B	A			N	101	1705	I
59	MAHESH	14134/20	30	M	SE	2	O	S	B	A	Y	N	N	N	N	N	N	N	N	A	A			N	112	5483	I
60	SWATI	13755/20	22	F	S	2	O	S	A	B	Y	N	N	N	N	N	N	N	N	A	A			N	92	5593	I
61	SHILPA	13598/20	33	F	HW	7	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		Y	176	200	I
62	ROHIT	13518/20	24	M	S	2	O	S	B	B	Y	N	N	N	N	N	N	N	N	A	A			N	108	8840	I
63	KALPNA	13435/20	30	F	HW	8	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		Y	102	200	I
64	PRABHAVATI	13220/20	23	F	S	4	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		N	87	200	I
65	SANGAYYA	13053/20	26	M	A	4	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	N	B	B			N	112	258	I
66	RUKMINI	13037/20	19	F	S	3	O	S	B	B	Y	N	N	N	N	N	N	N	N	A	A			N	98	6179	I
67	DYAMAKKA	12870/20	32	F	HW	4	O	S	B	C	Y	N	Y	N	Y	Y	N	N	N	B	A			N	73	2530	I
68	SONALI	12416/20	15	F	S	12	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		Y	195	212	I
69	BASAMMA	12383/20	27	F	HW	5	O	S	C	C	Y	N	Y	N	Y	Y	N	N	Y	B	B			N	97	307	I
70	YELLALING	11902/20	23	M	S	2	O	S	B	B	Y	N	N	N	N	N	N	N	N	A	A			N	91	4937	I
71	SYAPANASAB	10650/20	45	M	A	4	O	S	D	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	C	RF,CA		Y	171	306	D
72	SHRUTI	10017/20	25	F	S	4	O	S	B	C	Y	N	N	N	Y	Y	N	N	N	B	B			N	88	3679	I
73	ANKITA	7551/20	16	F	S	6	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B			N	89	248	I
74	RAVICHANDRAN	6723/20	19	M	S	7	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B			N	90	290	I
75	SAVITA	5860/20	27	F	HW	3	O	S	N	A	Y	N	N	N	N	N	N	N	N	A	A			N	121	5805	I
76	PALLAVI	4472/20	30	F	HW	5	O	S	C	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		N	105	363	I
77	DAVALBI	4010/20	20	F	HW	6	O	S	B	C	Y	N	Y	N	Y	Y	N	N	N	B	A			N	128	3032	I
78	IRAPPA	3945/20	55	M	A	11	O	S	D	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	B	RF		Y	178	200	I
79	POOJA	3830/20	15	F	S	5	O	S	B	B	Y	Y	Y	N	Y	N	N	N	N	B	A			N	84	1905	I
80	RENUKA	3455/20	28	F	HW	9	O	S	C	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	C	RF,CA		Y	217	1090	D
81	PUTTU ASHOK	2941/20	18	M	S	4	O	S	C	B	Y	Y	Y	N	Y	Y	N	N	N	B	B			N	99	2602	I
82	POOJA	1375/20	18	F	S	3	O	S	C	B	Y	Y	Y	N	N	Y	N	N	N	B	A			N	160	2776	I
83	PRATIKSHA	763/20	25	F	HW	6	O	S	C	C	Y	Y	Y	N	Y	Y	Y	N	Y	B	B			N	98	910	I
84	CHANDRAPPA	13935/20	52	M	A	6	O	S	D	C	Y	Y	Y	Y	Y	Y	N	N	Y	B	A	RF,CA		Y	243	200	D
85	LAXMI	13176/20	21	F	S	6	O	S	B	B	Y	N	Y	N	N	N	N	N	N	A	A			N	108	5719	I
86	MALLAMMA	15721/20	23	F	HW	5	O	S	B	B	Y	N	Y	N	N	N	N	N	N	A	A			N	95	5740	I
87	NAGESH	16136/20	40	M	A	6	O	S	B	C	Y	N	Y	N	Y	N	N	N	N	A	B			N	55	4518	I
88	SUJATA	13963/20	33	F	HW	4	O	S	B	B	Y	N	N	N	N	N	N	N	N	A	A			N	94	5955	I

89	IRAYYA	12393/20	22	M	A	3	O	S	B	B	Y	Y	N	N	Y	N	N	N	N	A	A			N	88	6087	I
90	SANGEETA	6678/20	30	F	HW	3	O	S	B	A	Y	N	N	N	N	N	N	N	N	A	A			N	87	6314	I
91	RENUKA	3428/20	35	F	HW	6	O	S	B	B	Y	N	Y	N	N	N	N	N	N	A	A			N	134	5232	I
92	ANIL	38166/18	37	M	A	6	O	S	B	C	Y	N	Y	N	Y	Y	N	N	N	B	B			N	86	2160	I
93	JAYASHREE	38946/18	33	F	HW	7	O	S	B	C	Y	Y	Y	N	Y	Y	N	N	Y	B	B	RF		N	177	1920	I
94	SATYAVVA	40517/18	38	F	A	5	O	S	C	B	Y	N	Y	N	Y	Y	N	N	N	B	B			N	143	3560	I
95	UMESH	4835/19	28	M	SE	7	O	S	B	C	Y	N	Y	Y	Y	Y	N	N	Y	B	B			N	138	1550	I
96	YALLAMMA	5283/19	44	F	A	4	O	S	B	B	Y	N	N	N	N	N	N	N	N	A	A			N	84	5390	I
97	RAMESH	13712/19	28	M	A	5	O	S	B	B	Y	Y	N	N	N	N	N	N	N	A	A			N	145	5600	I
98	ALMAS	18728/19	34	M	A	5	O	S	B	B	Y	Y	Y	N	N	N	N	N	N	A	A			N	95	5434	I
99	SAVITHA	6237/19	27	F	HW	4	O	S	B	B	Y	Y	N	N	N	N	N	N	N	A	A			N	82	6880	I
100	LAYAVVA	30293/18	46	F	A	4	O	S	B	C	Y	N	Y	N	N	N	N	N	N	A	A			N	80	6930	I