STUDY ON CO-RELATION BETWEEN SERUM ANTI-OXIDANT LEVELS AND THE CLINICAL MANIFESTATIONS IN PATIENTS WITH ORGANOPHOSPHORUS POISONING

Dissertation submitted to

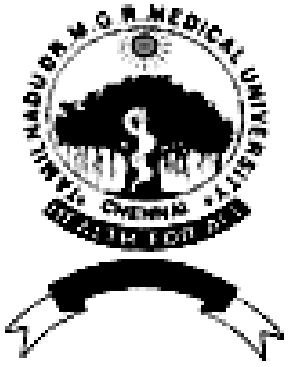
THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY

in partial fulfillment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE - I

DEGREE EXAMINATION



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CHENNAI – 600032

MARCH 2009

CERTIFICATE

This to certify that the dissertation entitled "**STUDY ON CO-RELATION BETWEEN SERUM ANTI-OXIDANT LEVELS AND THE CLINICAL MANIFESTATIONS IN PATIENTS WITH ORGANOPHOSPHORUS POISONING**" is a bonafide original work of **DR. MOHIT MATHUR,** in partial fulfillment of the requirements for M.D. Branch – I (Internal Medicine) Examination of the Tamilnadu Dr.M.G.R Medical University to be held in March 2009.

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DECLARATION

I, **Dr. MOHIT MATHUR,** solemnly declare that the dissertation titled, **"STUDY ON CO-RELATION BETWEEN SERUM ANTI-OXIDANT LEVELS AND THE CLINICAL MANIFESTATIONS IN PATIENTS WITH ORGANOPHOSPHORUS POISONING** " is a bonafide work done by me at Poison Control, Training and Research Center, Institute of Internal Medicine, Madras Medical College, during Jan 2008 to June 2008 under the guidance and supervision of **Prof. Dr. C. RAJENDIRAN, M.D.,** Institute of Internal Medicine. The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of M.D. Degree (Branch – I) in Internal Medicine.

Place: Chennai.

Date: **(Dr. MOHIT MATHUR)**

SPECIAL ACKNOWLEDGEMENT

I owe my thanks to the Dean, **Dr. T. P, KALANITI, M.D.,** Madras Medical College and Hospital, for granting me permission to conduct this study at the Institute of Internal Medicine attached to Madras Medical College and Government General Hospital.

ACKNOWLEDGEMENTS

The author finds it a pleasure to offer his special thanks to **Dr. C. RAJENDIRAN M.D.,** Director & Professor, Institute of Internal Medicine, Madras Medical College, Chennai for his dedicated invaluable guidance and constructive ideas during the study.

A special note of thanks to **Prof. P. Thirumalai Kolundu Subramanian** (Former Director Institute of Internal Medicine) for the advise and guidance given during the study.

The author is grateful to **Dr. R. MUTHUSELVAN M.D., Dr. S. BASKER M.D.,** Asst. Professors, Institute of Internal Medicine for the constant encouragement and timely guidance.

The author is very much indebted to **Dr. T. Thangam, Dr. V. Rajendiran, Dr. Ramesh, Dr. D. Thangam, Dr. Jeyakumar, Dr. G. Ravi,** Asst. Professors in Poison Control Treatment and Research Center, Government General Hospital, Chennai, who guided him during the course of the study.

The author wishes to express his gratitude to **Mr. Vijayakumar** Department of Bio-Chemistry for the help rendered during the study.

The author wishes to thank **Mr. Venkatesh,** Statistician, Madras Medical College, Chennai for the Assistance in the statistical analysis.

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1. INTRODUCTION

India is predominantly an agricultural country and the pesticides are essential for the farmers to ensure a good crop yield. This explains the easy and unrestricted availability of Organophosphorus compounds. Unfortunately people commonly use Organophosphorus compounds to commit suicide. They are extremely toxic substances with a very high mortality and morbidity. WHO estimates that about 3 million people are exposed to pesticide poisoning every year and causes about 3,00,000 deaths per year India has the highest incidence of patients with Organophosphorus poisoning in the world [1]. Circumstances of Organophosphorus poisoning :

- Intentional - 85.17 %
- Accidental - 4.7 %
- Occupational - 5.42 %

The case fatality of suicidal poisoning with OPC is 10-20%[1.] The primary reason for this being easy availability of Organophosphorus compounds.

Patient’s with Organophosphorus poisoning need specialized care, which exerts a large burden on the health care system and the society at large. The patients with OPC poisoning are usually physically normal otherwise and often they are the sole bread winners of their families. Hence any improvement in the treatment modality of OPC poisoning will benefit the society at large.

Oxidative stress is one of the myriad manifestations of OPC poisoning. The immediate and long term consequence of this Oxidative stress is still unknown. There is inadequate knowledge about the role of ant-oxidant supplements in a patient with OPC poisoning. It is never considered in the treatment strategies of patients with OPC poisoning.

In this study I propose to measure the Antioxidant levels in patients with OPC poisoning and to co-relate it with the clinical condition of the patient.

2. AIMS AND OBJECTIVES

- To classify and stratify the patients with Organophosphorus poisoning into different groups based on the severity of clinical features.

- To determine the Antioxidant levels in patients with OPC poisoning and to compare it with antioxidant levels in control patients.

- To analyze the co-relation between the severity of poisoning and the levels of Antioxidants.

- To analyze the co-relation between the type of OPC consumed and the level of of Antioxidants.

- To analyze the co-relation between Serum cholinesterase level and serum Antioxidant levels in a patient with OPC poisoning.

- To analyze the co-relation between RBC cholinesterase level and serum Antioxidant levels in a patient with OPC poisoning.

- To analyze the implication on the therapeutics based on the Antioxidant levels and the markers of Oxidative stress.

- To analyze the effect of treatment on the Antioxidant levels in patients with OPC poisoning

- To analyse the co-relation between the Outcome of the patient with OPC poisoning and the levels of Antioxidants.

3. REVIEW OF LITERATURE

3.1 HISTORY

Human beings have evolved into the most dominant species on this planet earth based on one important attribute of human nature – **Innovation**.

Human beings right through the course of history have been constantly innovating to make the world a more comfortable and safe place to live. We have manipulated the nature in such a way that we are able to use the natural resources for our benefit and development. As a result of this, the population of the world is growing in exponential numbers. To feed the billions of hungry mouths we needed to develop newer and more efficient ways to grow food crops. This constant and all pervasive need to improve our supply of food grains has compelled us to develop methods which increase the yield of food grains many fold.

Among these developments the development of pestcides is the most important. These pesticides are essential to prevent the food crops being destroyed by insects, fungi and animals. [2]

Pesticides are not new. Ancient Romans killed insect pests by burning sulfur and controlled weeds with salt. In the 1600s, ants were controlled with mixtures of honey and arsenic. By the late nineteenth century, U.S. farmers were using copper acetoarsenite (Paris green), calcium arsenate, nicotine sulfate and sulfur to control insect pests in field crops, but results were often unsatisfactory because of the primitive chemistry and application methods .[3,25,]

Among all the pesticides which were developed, the Oganophosphorus compounds revolutionized the agricultural field and paved the way for the Green revolution.

Organophosphate (OP) compounds are a diverse group of chemicals used in both domestic and industrial settings.

Organophosphate compounds were first synthesized in the early 1800s when **Lassaigne** reacted alcohol with phosphoric acid. Shortly thereafter in 1854**, Philip de Clermount** described the synthesis of tetraethyl pyrophosphate at a meeting of the French Academy of Sciences[4].

Eighty years later**, Lange**, in Berlin, and, **Schrader**, a chemist at Bayer AG, Germany, investigated the use of organophosphates as insecticides. However, the German military prevented the use of organophosphates as insecticides and instead developed an arsenal of chemical warfare agents (ie, tabun, sarin, soman).[5] A fourth agent, VX, was synthesized in England a decade later. During World War II, in 1941, organophosphates were reintroduced worldwide for pesticide use, as originally intended.

Massive organophosphate intoxication from suicidal and accidental events, such as the Jamaican ginger palsy incident in 1930, led to the discovery of the mechanism of action of organophosphates. In 1995, a religious sect, **Aum Shinrikyo**, used **sarin** to poison people on a Tokyo subway. [6]

Nerve agents have also been used in battle, notably in Iraq in the 1980s. Additionally, chemical weapons still pose a very real concern in this age of terrorist activity. According to WHO stastics Poisoning by Pesticides comprise about 30% of all causes of deliberate self harm in India[1].

3.2. CHEMISTRY AND BIOLOGICAL EFFECTS OF ORGANOPHOSPHORUS COMPOUNDS

Organophosphates (OP) are cholinesterase-inhibiting chemicals used predominately as pesticides. They are also used as chemical warfare agents (nerve agents). OPs include all insecticides containing phosphorous derived from phosphoric acid, and are generally the most toxic of all pesticides to vertebrate animals.

OPs and carbamates inhibit the function of carboxylic ester hydrolases, such as chymotrypsin, acetylcholinesterase (AChE), plasma or butyrilcholinesterase (BuChE), plasma and hepatic carboxylesterases (aliesterases), paraoxonases (esterases), and other nonspecific esterases within the body. [14, 15, 16, 17, 18],The most prominent clinical effects of poisoning with OPs result from their inhibition of AChE .

Organophosphates can be absorbed cutaneously, ingested, inhaled, or injected. Although most patients rapidly become symptomatic, the onset and severity of symptoms depend on the specific compound, amount, route of exposure, and rate of metabolic degradation.

Classification of OPC agents based on leaving group [19]

Group 1: Phosphorylcholines	Subsituted quartenary N	Echothiopate
Group 2: Fluorophosphates	Fluoride	Dimefox, sarin.
Group 3: cyanophosphates/ Halophosphates	CN, SCN, OCN	Tabun.
Group 4: multiple constituents "R group"	Dimethoxy	Chlorothion, Methylparathion Dichlorvos, Fenthion Temephos, Malathion
	Diethoxy	Chlorfenvinphos, Ethion, Phorate, TEPP, diazinon, Parathion, Coumaphos
	Dialkoxy	Isopropyl paraxoan
	Diamino	Schradan
	Chlorinated/ dialkoxy	Haloxan
	Trithioalkyl	Merphos
	Triphenyl	TOCP

General structure of OPC compounds [19]

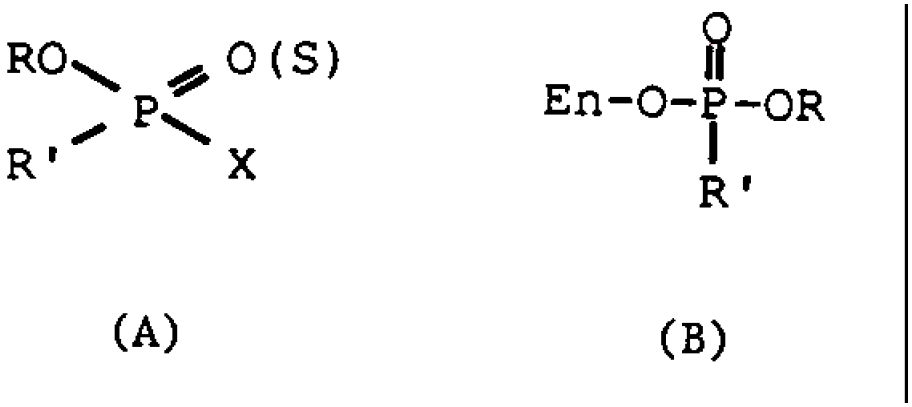

Fig : 1

3.3. PATHOPHYSIOLOGY OF OPC POISONING

The primary mechanism of action of organophosphate pesticides is inhibition of carboxyl ester hydrolases, particularly acetylcholinesterase (AChE). AChE is an enzyme that degrades the neurotransmitter acetylcholine (ACh) into choline and acetic acid. ACh is found in the central and peripheral nervous system, neuromuscular junctions, and red blood cells (RBCs).

Organophosphates inactivate AChE by phosphorylating the serine hydroxyl group located at the active site of AChE. The phosphorylation occurs by loss of an organophosphate leaving group and establishment of a covalent bond with AChE. [6]

Once AChE has been inactivated, ACh accumulates throughout the nervous system, resulting in overstimulation of muscarinic and nicotinic receptors. Clinical effects are manifested via activation of the autonomic and central nervous systems and at nicotinic receptors on skeletal muscle. Once an organophosphate binds to AChE, the enzyme can undergo 1 of the following 3 processes:

- Endogenous hydrolysis of the phosphorylated enzyme by esterases or paraoxonases
- Reactivation by a strong nucleophile such as pralidoxime (2-PAM) [6]
- Complete binding and inactivation (aging)

Table 1- Clinical manifestations of acute Organophosphate Poisoning

4, 21-25

MUSCARINIC	NICOTINIC	NERVOUS SYSTEM
▪ Diarrhoea ▪ Urinary incontinence ▪ Miosis ▪ Bradycardia ▪ Bronchorrhoea ▪ Bronchoconstriction ▪ Salivation ▪ Lacrimation ▪ Emesis ▪ Hypotension ▪ Cardiac arrhythmias	▪ Fasciculations ▪ Tremors ▪ Muscle weakness with respiratory failure ▪ Hypertension ▪ Tachycardia ▪ Sweating ▪ Mydriasis	▪ Altered sensorium. ▪ Seizures. ▪ Tremors ▪ Type 1 paralysis (Acute cholinergic crisis) ▪ Type 2 paralysis (Intermediary syndrome) ▪ Type 3 paralysis (Delayed OPC induced neuropathy)

Table 2- Peradeniya organophosphate poisoning score

Parameter		score
Miosis		
	Pupils > 2mm	0
	Pupils ≤ 2mm	1
	Pupils pin-point	2
Fasciculation		
	None	0
	Present	1
	Generalized/ continuous & cyanosis	2
Respiration		
	≤ 20/ min	0
	> 20/ min	1
	> 20/ min & cyanosis.	2
Heart rate		
	> 60 /min	0
	41-60 /min	1
	≤40 /min	2
Level of consciousness		
	Conscious / alert	0
	Impaired, responds to verbal commands	1
	No response to verbal commands	2
	Convulsions	+1

Total score (Max score – 11)

3.4 OXIDATIVE STRESS AND ANTIOXIDANTS

FREE RADICALS

It is ironic that oxygen, an element indispensable for life, under certain situations has deleterious effects on the human body. Most of the potentially harmful effects of oxygen are due to the formation and activation of a number of chemical compounds, known as reactive oxygen species, which have a high tendency to donate oxygen to other substances.[7,8,9]

Many such reactive species are free radicals, i.e. molecules with one or more unpaired electrons and therefore unstable and highly reactive. Free radicals have various chemical structures, such as hydroxyl, superoxide, nitric oxide and lipid peroxyl radicals.

Seeking stability, radicals attack nearby molecules to obtain another electron and this damage the structure and function of the molecule.

If free radicals are not inactivated, their chemical reactivity can damage all cellular macromolecules, including proteins, carbohydrates, lipids and nucleic acids Free radicals have the ability to change the

structure of DNA and serve as a precursor of cancer by inducing genotoxicity.

Free radicals and other reactive oxygen species are derived either from normal essential metabolism in the human body or from external sources, such as exposure to rays, ozone, cigarette smoking, certain drugs, pesticides, air pollutants and industrial chemicals.

Free radical formation occurs continuously in cells as a consequence of both enzymatic and non-enzymatic reactions.

The balance between the production of free radicals and antioxidant defenses in the body has important health implications: if there are too many free radicals or too few antioxidants for protection, a condition of oxidative stress develops, which may cause chronic and permanent damage.

ANTIOXIDANTS

The human body has several mechanisms to counteract the damage caused by free radicals. The basic and the most prominent defense mechanism of the human body is antioxidant agents. The term antioxidant has been defined as any substance that delays or inhibits oxidative damage to a target molecule. These molecules are stable enough to neutralize free radicals by donating electrons. Today many compounds have been found to have antioxidant activity, but in the human body they can be categorized in two main systems. The main system of defense against damage from free radicals is the enzymatic system that opposes oxidation. [27-32]

The body maintains pools of the antioxidant vitamins, such as vitamin E, vitamin C, and beta-carotene, the vitamin A precursor. This first defense system tries to handle all free radicals, but if the oxidative stress is far greater than the capacity of the system, the second line of defense (vitamins) may come into play. Vitamins scavenge and quench free radicals, but are oxidized and inactivated in the process. Each of these antioxidant nutrients has specific activities, and they often work synergistically to enhance the overall antioxidant capacity of the body[27].

3.5 PESTICIDES AND OXIDATIVE STRESS

The widespread use of Organophosphorus compound pesticides in public health and agricultural programs has caused severe environmental pollution and health hazards, including cases of severe acute and chronic human poisoning . The introduction of new, more toxic and rapidly disseminating Organophosphorus compound pesticides into the environment has necessitated accurate identification of their potential hazards to human health.

These toxic chemicals have become an integral part of the ecosystem, although many of them are extremely toxic to mammals and other non-target creatures. However, the implications of pesticide residues for human health have yet to be comprehensively documented.[27]

Free radicals play an important role in the toxicity of Organophosphorus compound pesticides and environmental chemicals , they may induce oxidative stress, leading to generation of free radicals and alteration in antioxidants, oxygen free radicals, the scavenging enzyme system, and lipid peroxidation.

Several studies have demonstrated oxidative stress induced by OPs in rats and humans. It is reported that OPIs, besides their inhibitory effect on AChE, also induce changes characteristic of oxidative stress.

Superoxide dismutase (SOD), whose substrate is a free radical (superoxide anion; O2•-) catalyzes dismutation reaction resulting in the generation of hydrogen peroxide (H2O2). This H2O2 is decomposed to water and molecular oxygen by the action of catalase. When the free radical production overwhelms the endogenous antioxidant levels, they cause considerable cell damage/death.

All the major biomolecules like lipids, proteins, and nucleic acids may be attacked by free radicals, but lipids are probably the most susceptible.The oxidative destruction of lipids (lipid peroxidation) is a destructive, self-perpetuating chain reaction, releasing malonyl dialdehyde (MDA) as the end product. ***M. Dandapani*** *et al* [20] have proposed oxidative stress as a causative factor in the pathogenesis of Intermediary syndrome. ***Vidyasagar J et al***[27] proposed the role of oxidative stress in their study of patients with OPC poisoning.

Pena-Llopis, Samuel had proposed that Antioxidants can be used as safe adjuntive treatment in patients with Organophosphorus Poisoning

in the article ‘Antioxidants as Potentially Safe Antidotes for Organophosphorus Poisoning.’ [26]

In view of the possible oxidative stress involved in OPC Poisoning, the levels of SOD, MDA, Total Antioxidants, RBC cholinesterase, Serum Pseudocholinesterase levels were determined as an index of antioxidant status and oxidative stress.

4. MATERIALS AND METHOD

SETTING

The study was conducted at the Poison Control, Training and Research Centre of Madras Medical College and Government General Hospital, Chennai.

DESIGN OF STUDY: Descriptive.

PERIOD OF STUDY: Jan 2008 to June 2008.

ETHICAL CLEARENCE: Obtained.

INFORMED CONSENT

Informed consent from all the patients / attendants was obtained.

MATERIALS

All patients admitted with isolated Organophosphorus Poisoning , during the study period were included in the study .

INCLUSION CRITERIA

All patients with OPC poisoning admitted during the study period. The poisoning with OPC compounds was confirmed by detailed history,

physical examination, circumstantial evidence like container, witness etc . The diagnosis was supported by appropriate lab tests like - Gastric aspirate analysis for OPC by Thin layer Chromatography.

EXCLUSION CRITERIA

a) Patients with associated poisoning with any other substance like Alcohol, Organochlorines, Oduvanthalai, Sedatives, Recreational drugs, etc.

b) Patients/attendants refusing to consent for the study.

c) Patients with known medical illness such as neuromuscular disorders like myasthenia gravis or muscular dystrophy, hypokalemic periodic paralysis and conditions known to alter biochemical parameters were excluded.

METHOD

a) The patients with confirmed & isolated OPC poisoning were clinically examined at admission and detailed history was taken.

b) The patient's Peradeniya Organophosphorus poisoning score was calculated at admission on Day 1.

c) The patients' blood (5 ml of serum) was drawn for the estimation of Antioxidant levels and for other markers of Oxidative stress like Superoxide Dismutase, Catalase, Glutathione Reductase, Glutathione transferase on Day 1 using UV- Spectrophotometer.

d) Simultaneous blood samples were drawn from age, sex and geographically matched healthy volunteers and antioxidant levels was estimated in them as control.

e) The patients' blood (2ml serum) was drawn on Day 1 to estimate the Serum Cholinesterase and RBC Cholinesterase levels.

f) Simultaneous blood samples were drawn from age, sex and geographically matched healthy volunteers and Serum Cholinesterase and RBC Cholinesterase levels was estimated in them as control.

g) The patient was treated with standard protocol treatment for OPC poisoning and supportive treatment like Mechanical Ventilation etc was instituted as necessary.

h) The Peradeniya Organophosphorus poisoning score of the patient was determined on Day 3 and Day 5.

i) The patients antioxidant levels and Superoxide Dismutase, Catalase, Glutathione Reductase, Glutathione transferase were repeated on Day 5.

j) The Serum Cholinesterase and RBC Cholinesterase levels were estimated on Day 5.

k) The results were collated and analysed using standard descriptive analysis methods.

5. OBSERVATIONS AND RESULTS

Data were analyzed using SPSS 6.0. All continuous variables were analyzed using Mann Whitney U test, student-t test, discrete variables using Chi-square test (Fisher's Exact Probability Test).

Table 3- Type of Poison with outcome Cross-tabulation

Type of Poison	Outcome		Total
	Improved	Death	
CHLORPYRIPHOS	3	1	4
DIMECRON	6	2	8
DIMETHOATE	2	1	3
FOLIDOL	12	3	15
METAPHOS	1	0	1
MONOCROTOPHOS	8	4	12
PARATHION	3	1	4
PHORATE	2	1	3
TOTAL	**37**	**13**	**50**

Analysis of the type of OPC compound consumed showed that Folidol was the most commonly used compound - 12/50 i.e 24%, followed by Monocrotophos - 8/50 i.e 16%. There were 13 deaths out of total 50 patients i.e 26%. The maximum deaths were due to Monocrotophos - 4/13 i.e 30.2%.

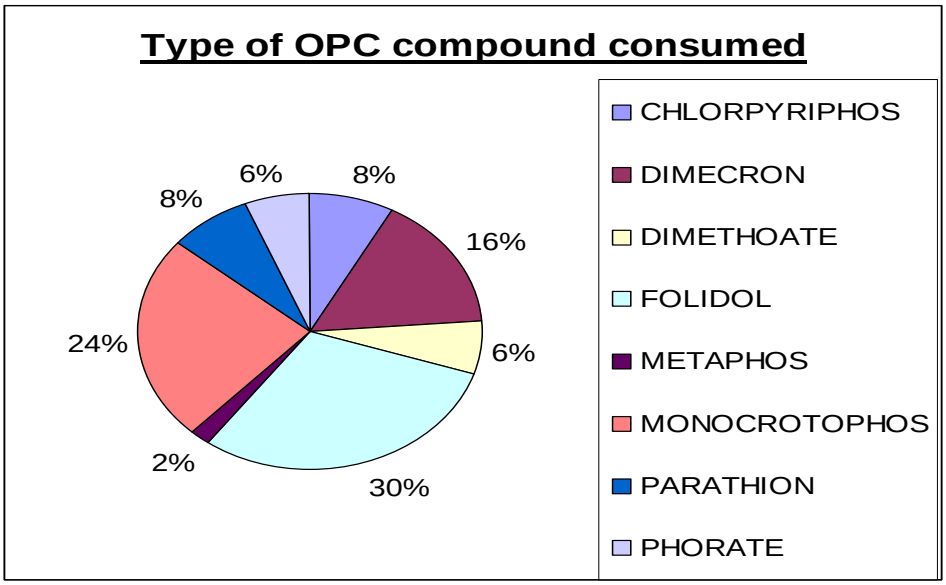
Type of OPC compound consumed
8%
16%
6%
30%
2%
24%
8%
6%
CHLORPYRIPHOS
DIMECRON
DIMETHOATE
FOLIDOL
METAPHOS
MONOCROTOPHOS
PARATHION
PHORATE

Fig : 2

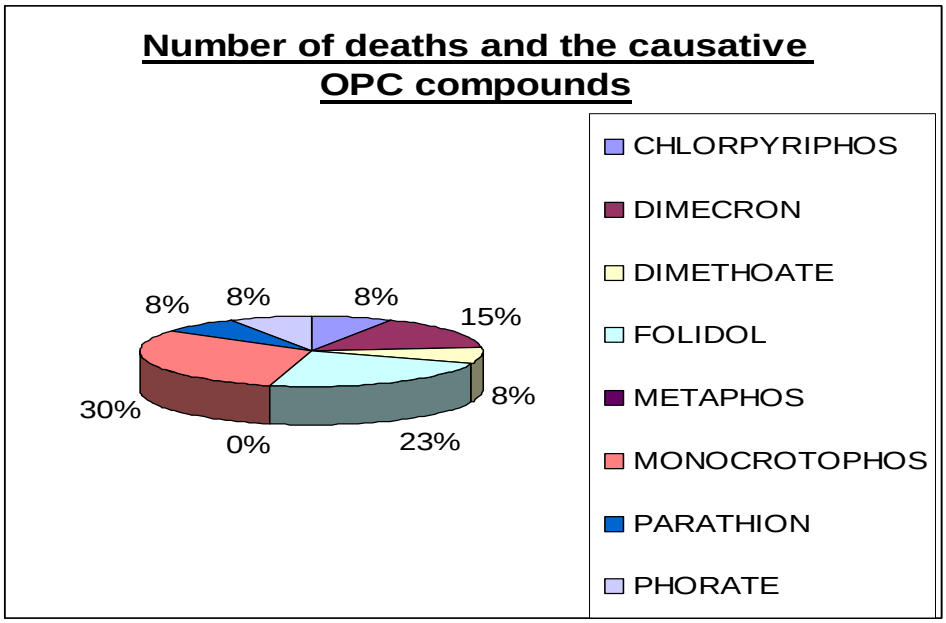
Number of deaths and the causative OPC compounds
8%
8%
8%
15%
8%
23%
0%
30%
CHLORPYRIPHOS
DIMECRON
DIMETHOATE
FOLIDOL
METAPHOS
MONOCROTOPHOS
PARATHION
PHORATE

Fig : 3

Table 4 - Quantity of OPC consumed by the patients

	Outcome	N	Mean	Student independent t-test
Quantity (ml)	Improved	37	60.65	t=3.33 P=0.01 significant
	Death	13	179.23	

The patients who survived OPC poisoning had consumed 60.65 ml (mean) and the patients who expired had consumed 179.23 ml (mean).

The p value was 0.01. The difference in the quantities consumed was stastically significant.

Table 5 - Duration of Hospital stay

The mean duration of hospital stay among the two groups of patients is as follows.

	Outcome	**N**	**Mean**	**Student independent t-test**
Hospitalization (Days)	Improved	37	7	t=1.45 P=0.15 not significant
	Death	13	9	

The mean duration hospital stay among the patients who improved was 7 days, the duration was 9 days in patients who expired. The difference in the duration of hospital stay was not stastically significant.

Table 6 - Peradeniya Organophosphorus Poisoning (POP)scale : Comparision between scores on Day 1 and Day 5

	Outcome	n	Mean
POP Day 1	Improved	37	5
	Death	13	9
POP Day 5	Improved	37	4
	Death	13	7

The Peradeniya Organophosphorus poisoning scale was calculated in all patients. The mean POP score on Day 1 in patients with poisoning who survived was 5/11 and 4/11 on Day 5. The mean POP score on Day 1 in patients with poisoning who expired was 9/11 and 7/11 on Day 5.

The POP score was significantly higher in patients who succumbed to OPC poisoning.

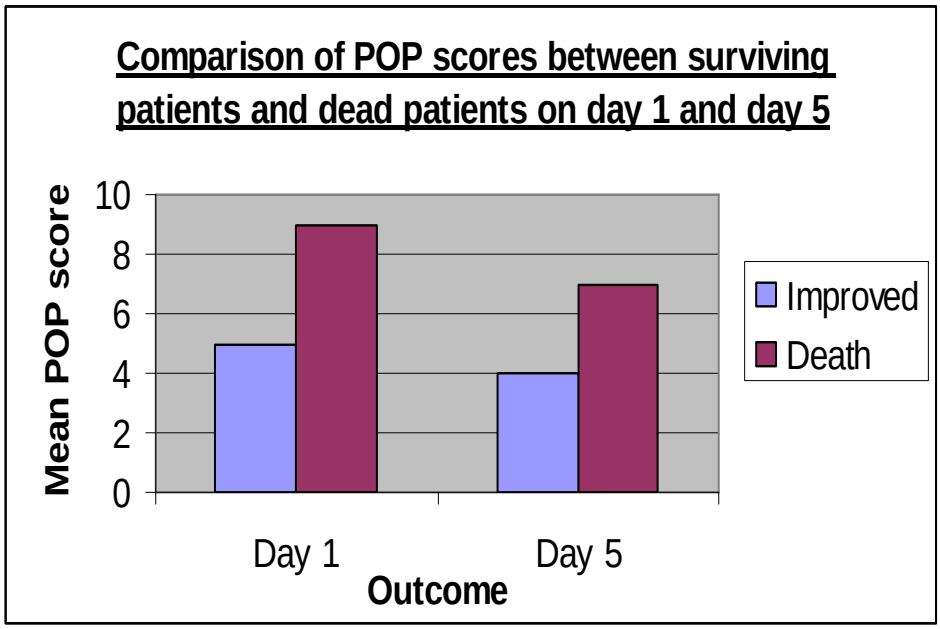
Comparison of POP scores between surviving patients and dead patients on day 1 and day 5
Mean POP score
10
8
6
4
2
0
Day 1
Day 5
Outcome
Improved
Death

Fig : 4

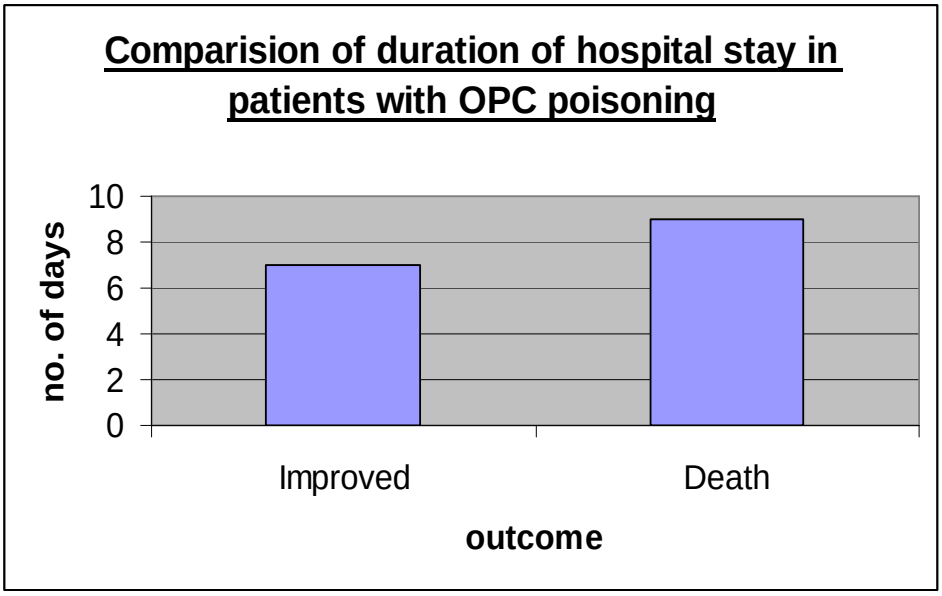
Comparision of duration of hospital stay in patients with OPC poisoning
no. of days
10
8
6
4
2
0
Improved
Death
outcome

Fig: 5

Table – 7 Comparision between Antioxidant levels in patients with OPC poisoning and Normal controls

Parameter studied	GROUP		Student independent t-test	
	Study Group N = 50	Control Group N = 30	T	p - value
TotTotal Antioxidants m.mol/L)	1.66 +/- 0.14	0.94 +/- 0.10	25.64	0.001
SOD (mic.mol/Hb gm%)	7.47 +/- 1.06	4.53 +/- 0.70	13.64	0.001
CATALASE (mic.mol/Hb gm%)	5.54 +/- 0.81	2.92 +/-0.56	15.49	0.001
Glutathione Reductase (mic.mol/Hb gm%)	11.00 +/- 1.32	9.58 +/-0.56	5.52	0.001
Glutathione Transferase (mic.mol/Hb gm%)	6.02 +/- 0.66	5.02 +/- 0.87	5.78	0.001

The antioxidant levels were compared between Healthy controls and the Patients. As evident from the table above all the antioxidants were increased in the patients with OPC poisoning . The Total Antioxidants in control was 0.94 +/- 0.10 SD. This was significantly higher in patients with OPC poisoning 1.66 +/-0.14. Similarly all the Antioxidant levels measured were increased in patients with OPC poisoning. p – value was less than 0.001 in all the measured parameters.

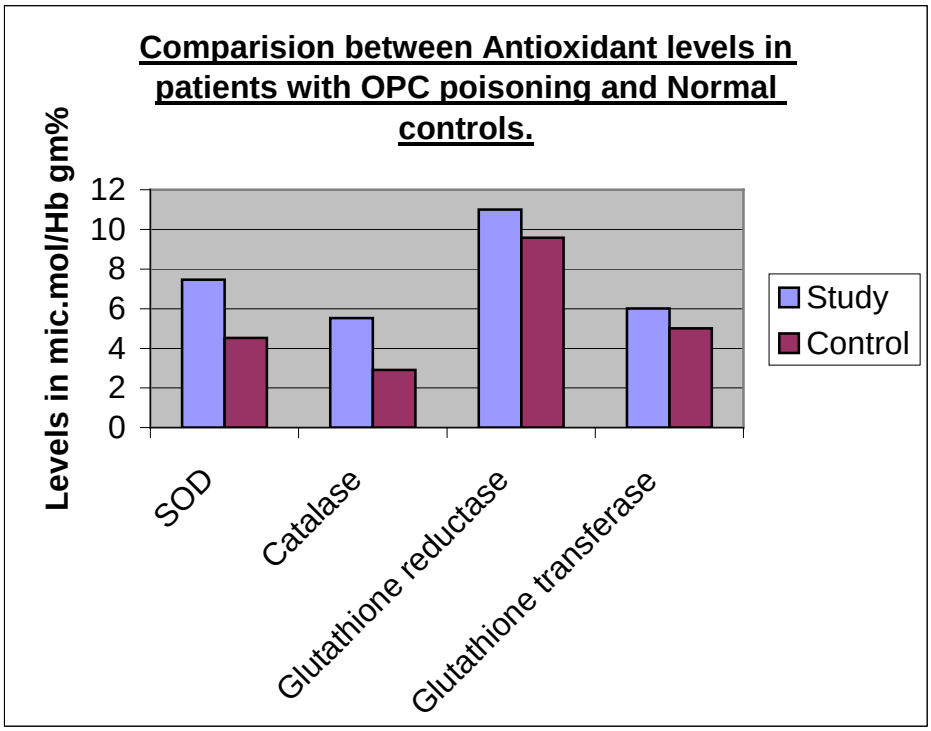
Comparision between Antioxidant levels in patients with OPC poisoning and Normal controls.
Levels in mic.mol/Hb gm%
12
10
8
6
4
2
0
SOD
Catalase
Glutathione reductase
Glutathione transferase
Study
Control

Fig : 6

Table – 8 Comparision between MDA levels in patients with OPC poisoning and Normal controls

Parameter studied	GROUP		Student independent t-test	
	Study Group n= 50	Control Group N = 30	t-value	p - value
MDA (n.mol/ml)	2.10 +/- 0.65	1.25 +/- 0.08	7.09	0.001

The MDA levels were 2.10 +/- 0.65 in the patients with OPC poisoning and 1.25 +/- 0.08 in normal controls. The levels were significantly elevated in patients with OPC poisoning.

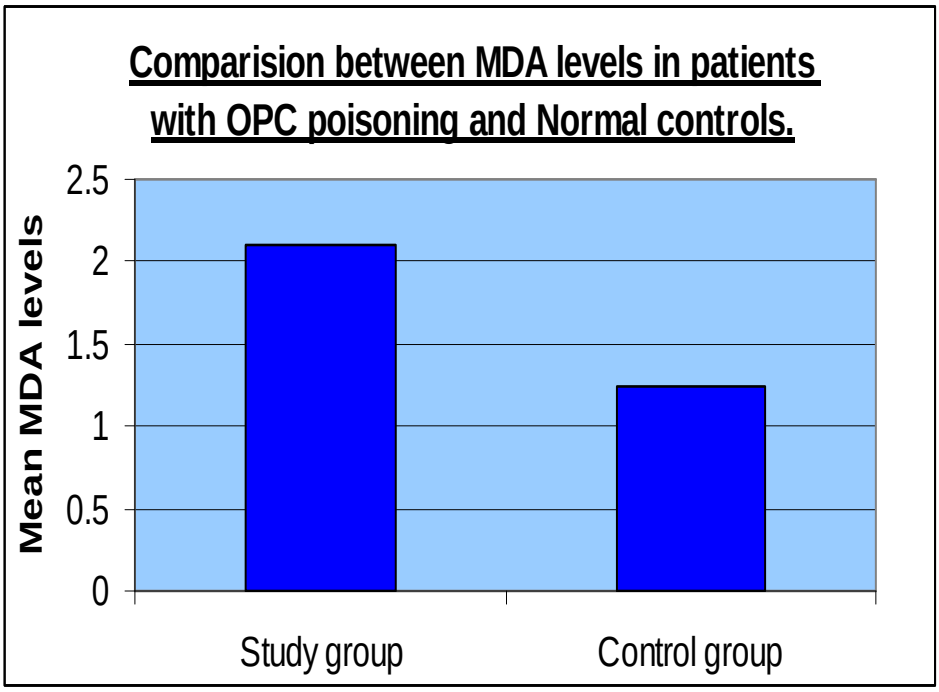
Comparision between MDA levels in patients with OPC poisoning and Normal controls.
Mean MDA levels
2.5
2
1.5
1
0.5
0
Study group
Control group

Fig : 7

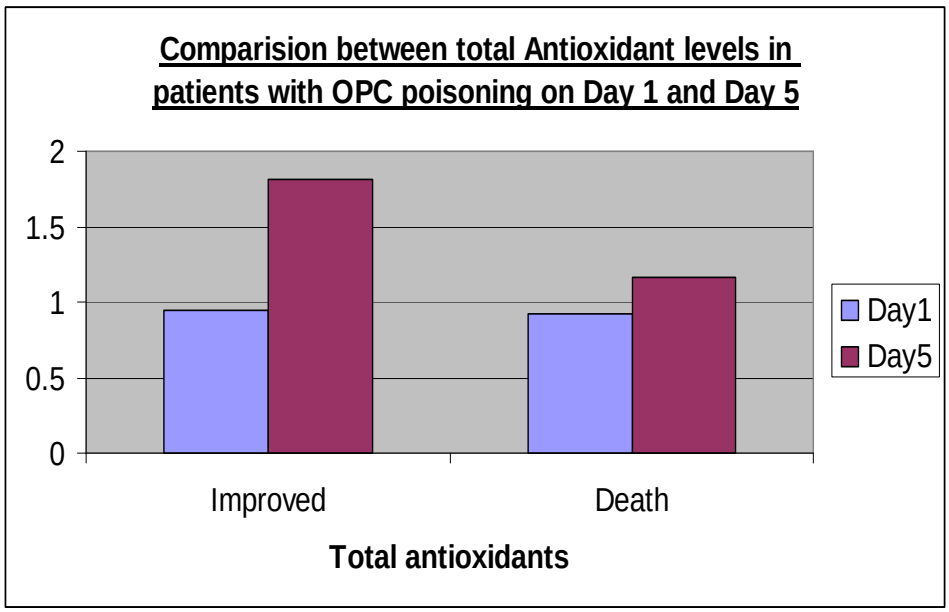
Comparision between total Antioxidant levels in patients with OPC poisoning on Day 1 and Day 5
2
1.5
1
0.5
0
Improved
Death
Total antioxidants
Day1
Day5

Fig : 8

Table 9 - Comparision between Antioxidant levels in patients with OPC poisoning on Day 1 and Day 5

	Outcome	N	Mean	Std Deviation	Student independent t-test
Total Antioxidants D 1	Improved	37	0.95	0.10	0.01
	Death	13	0.92	0.08	0.02
Total Antioxidants D 5	Improved	37	1.81	0.37	0.06
	Death	13	1.17	0.27	0.07
SOD D 1	Improved	37	7.58	1.13	0.18
	Death	13	7.17	0.78	0.21
SOD D 5	Improved	37	6.63	0.58	0.09
	Death	13	6.51	0.47	0.13
CATALASE D 1	Improved	37	5.57	0.77	0.21
	Death	13	5.53	0.84	0.13
CATALASE D 5	Improved	37	4.28	0.59	0.09
	Death	13	4.23	0.60	0.16
Glutathione Reductase D 1	Improved	37	10.73	1.21	0.33
	Death	13	11.09	1.36	0.22
Glutathione Reductase D 5	Improved	37	9.13	0.54	0.09
	Death	13	8.99	0.72	0.20

	Outcome	N	Mean	Std Deviation	Student independent t-test
Glutathione Transferase D 1	Improved	37	6.08	0.66	0.10
	Death	13	5.84	0.66	0.18
Glutathione Transferase D 5	Improved	37	5.24	0.29	0.05
	Death	13	5.03	0.53	0.14

The Antioxidant levels were increased in all the patients with OPC poisoning. The Antioxidant levels were higher on Day 1 than Day 5. the difference between the levels of Antioxidants on Day 1 and Day 5 was not significant. The difference in the increased Antioxidant levels between patients who improved and the patients who died was also not significant.

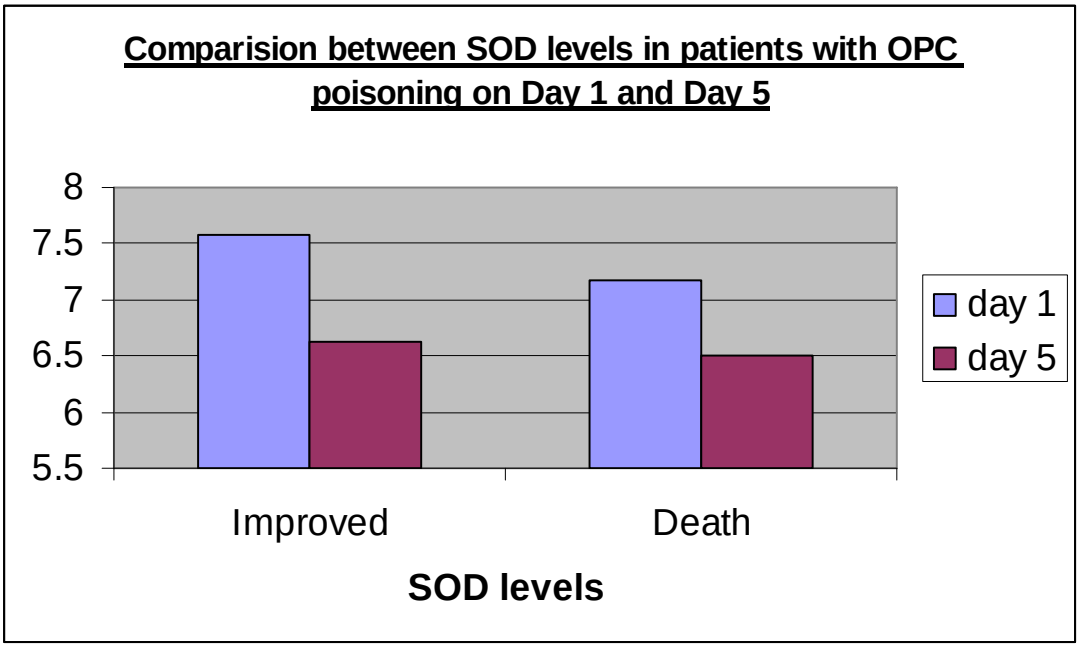
Comparision between SOD levels in patients with OPC poisoning on Day 1 and Day 5
8
7.5
7
6.5
6
5.5
Improved
Death
SOD levels
day 1
day 5

Fig : 9

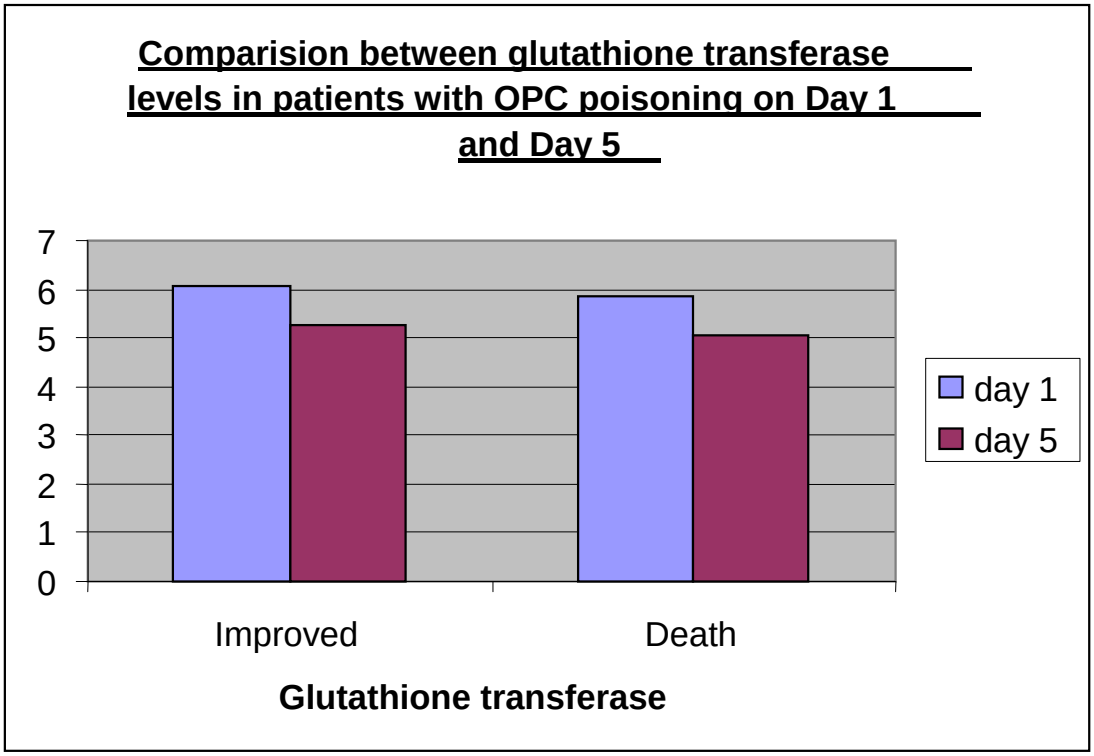
Comparision between glutathione transferase levels in patients with OPC poisoning on Day 1 and Day 5
7
6
5
4
3
2
1
0
Improved
Death
Glutathione transferase
day 1
day 5

Fig : 10

Table 10 - Comparison of RBC Cholinesterase levels on Day 1 and Day 5 between patients who improved and those who expired

	Outcome	**N**	**Mean**	**Std. Deviation**	**Student independent t-test**
RBC Cholinesterase (mcg/ml) D 1	Improved	37	145.68	10.79	1.77
	Death	13	145.92	9.14	2.53
RBC Cholinesterase (mcg/ml) D 5	Improved	37	216.54	46.27	7.60
	Death	13	229.62	44.93	12.46

The RBC Cholinesterase levels were reduced on Day 1 in both group of patients and they had increased on day 5 in both group of patients. The difference in the RBC Cholinesterase levels between the patients who improved and the patients who expired was not significant.

Table 11 - Comparison of Plasma Cholinesterase levels on Day 1 and Day 5 between patients who improved and those who expired

Parameter	Outcome	N	Mean	Std. Deviation	Student independent t-test
Pl. Cholinesterase D1 (mcg/ml.)	Improved	37	65.43	11.13	1.83
	Death	13	59.31	7.46	2.07
Pl Cholinesterase D 5 (mcg/ml.)	Improved	37	125.92	18.13	2.98
	Death	13	134.62	21.04	5.83

The Plasma Cholinesterase levels were reduced on Day 1 in both group of patients and they had increased on day 5 in both group of patients. The difference in the Plasma Cholinesterase levels between the patients who improved and the patients who expired was not significant.

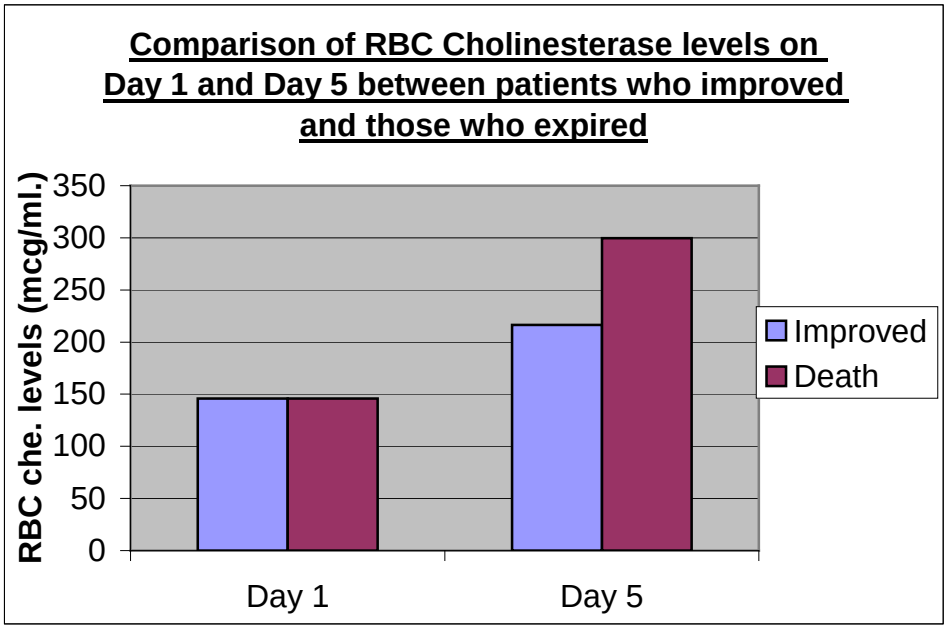
Comparison of RBC Cholinesterase levels on Day 1 and Day 5 between patients who improved and those who expired
RBC che. levels (mcg/ml.)
350
300
250
200
150
100
50
0
Day 1
Day 5
Improved
Death

Fig: 11

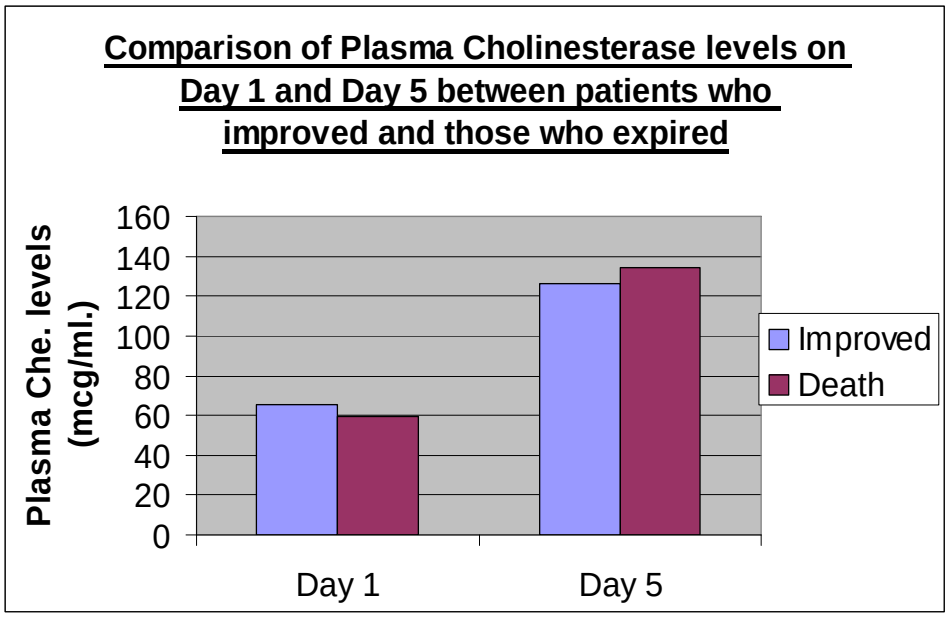
Comparison of Plasma Cholinesterase levels on Day 1 and Day 5 between patients who improved and those who expired
Plasma Che. levels (mcg/ml.)
160
140
120
100
80
60
40
20
0
Day 1
Day 5
Improved
Death

Fig: 12

6. DISCUSSION

The Organophosphorus compounds are one of the commonly used methods to commit suicide in India. Extensive work has been done Worldwide on the various aspects of the Organophosphorus compound poisoning, including the socio-demographic, clinico-pharmacological profile, treatment and outcome modalities. Since OPC poisoning is one of the predominant causes of suicides in India and other developing countries, any improvement in our knowledge about the management of OPC poisoned patient will go a long way in reducing the high mortality and morbidity associated with OPC poisoning.

In this study conducted at the Poison Control Treatment and Research center of Govt General Hospital, Chennai, apart from the routine socio-demographic and clinical profile of the OPC poisoned patients, the Anti-oxidants levels of the patient and the RBC cholinesterase and Plasma cholinesterase levels of the patients were estimated using UV-spectrophotometry and their levels were compared with that of normal healthy controls. The Anti-oxidants levels of the patient and the RBC cholinesterase and Plasma cholinesterase levels were estimated on Day 1(at the time of admission) and on Day 5.

In this study the clinical profile of the OPC patients were classified using the Peradeniya Organophosthorus-Poisoning(POP scale). This scale was developed in the University of Peradeniya, Srilanka. The advantage of this scale over other scales like Modified Drieshbach's Criteria etc, is that this score is more accurate and even minor changes in the clinical condition of the patient with OPC poisoning can be detected and recorded for comparison. With the help of this scoring, the prognosis and the course of the patient can be accurately monitored.

In this study I have attempted to correlate the Peradeniya Organophosthorus-Poisoning(POP scale) score of the patients with the Serum anti-oxidants levels and the RBC, Plasma Cholinesterase levels.

In this study the confounding factor in the estimation of serum anti-oxidant levels could be the patients underlying general health condition. Many diseases like Diabetes Mellitus, Hypertension, Metabolic syndrome, Neuro-degenerative disorders like Alzheimer's disease can have alteration in the antioxdants levels [23]. Other factors like smoking, alcoholism, drug abuse, exposure to environmental pollutants can also increase the oxidative stress in the human body [21,22,24].

In the study conducted 50 patients with confirmed and isolated OPC poisoning were included. Patients with multiple, mixed poisonings were excluded. The patients on admission received the routine treatment protocol for OPC poisoning. They received Inj. Atropine, Inj. P_2AM, supportive measures like body wash, Bowel decontamination, Mechanical ventilation etc.

6.1 Peradeniya Organophosphorus poisoning (POP) score

The Peradeniya Organophosphorus poisoning score (POP) was calculated in all the patients at admission, day 5 and in between. Out of the 50 patients studied 37 survived and 13 succumbed. The mean POP score among survivors was 5/11 on day 1 and 4/11 on day 5. The mean POP score in the patients who died was 9/11 on day 1 and 7/11 on day 5. The difference in the POP score between the survivors and the patients who died was significant. A higher score was indicative of increased mortality, morbidity and the need for mechanical ventilation. Hence, POP score can be used in all patients with OPC poisoning to predict the outcome and course of hospital stay. It is better than modified Drieshbach's criteria, Namba-scoring in predicting the outcome and course of hospital stay[14].

6.2 Total Anti-oxidant levels

The mean total Anti oxidants levels among the patients with OPC poisoning was 1.66 m.mol/L and in normal controls was 0.94 m.mol/L. The anti-oxidants levels in the patients with OPC poisoning was significantly elevated when compared to normal controls. The total anti-oxidant levels of patients on day 1 and day 5 was measured. The mean total anti oxidant levels in the patients who improved was 0.95 m.mol/L +/- 0.10 SD on day 1 and 1.81 m.mol/L +/-0.37 SD on day 5. The mean total anti oxidant levels in the patients who expired was 0.92 m.mol/L +/- 0.08 SD on day 1 and 1.17 m.mol/L +/- 0.27 SD on day 5.

The anti-oxidants levels were elevated significantly due to the oxidative stress produced by the OPC compounds. In condition of acute oxidative stress, this is a defense mechanism of the body.

However, the severe oxidative stress due to OPC compounds overwhelms the anti-oxidants capacity of the body and eventually there is a decline in the anti-oxidant levels. Hence, in contrast to acute OPC poisoning the anti-oxidant levels in chronic OPC poisoning is reduced.

In a study by ***Surapaneni et al*** [37,38] It was observed that there was a significant increase in erythrocyte MDA levels; SOD, GPX and plasma

GST activities; and a significant decrease in erythrocyte GSH, ascorbic acid, plasma vitamin E levels and catalase activity in patients with Chronic diseases like Diabetes Mellitus, Osteoarthritis etc when compared to controls. They concluded that the increased activities of antioxidant enzymes may be a compensatory regulation in response to increased oxidative stress.

There was no significant difference in the anti-oxidants levels between OPC survivors and expired patients. This could be due to the fact that even non-fatal quantities of OPC compounds can cause significant oxidative stress. This finding reinforces the importance of oxidative stress in OPC poisoning.

6.3 Individual Anti-oxidant levels ; (SOD, Catalase, GSH, GR)

Super oxide dismutase levels (SOD), catalase, Glutathione Reductase, Glutathione Transferase levels were measured ,the levels of these anti-oxidants were significantly elevated in patients with OPC poisoning when compared with normal healthy controls. The patients super oxide dismutase levels (SOD), catalase, Glutathione Reductase, Glutathione Transferase levels were measured on day 1 and day 5. They were significantly elevated, however the difference between day 1 and

day 5 levels was statistically insignificant. This is probably due to the long duration of oxidative stress produced by the OPC poisons.

In a study ***Changes in antioxidant enzymes in humans with long-term exposure to pesticides by Olga López et al*** [39], a cohort of 81 intensive agriculture workers (pesticide sprayers) was assessed twice during the course of a spraying season for changes in erythrocyte antioxidant enzymes. Acetylcholinesterase (AChE) was used as a reference biomarker. Sprayers presented lower levels of superoxide dismutase (SOD) and glutathione reductase (GR) as compared to controls independently of age, BMI, smoking habit or alcohol consumption. In their study they found that Paraoxonase (PON1) polymorphism influenced erythrocyte Catalase and Glutathione Reductase, as subjects with the R allele presented lower Catalase and higher Glutathione Reductase levels. Similar studies have been were reported by workers from India also, a study by ***A. Prakasam et al,Plasma and RBCs antioxidant status in occupational male pesticide sprayers*** [34], done in Annamalai,Tamil Nadu, had different conclusions. The concentration of antioxidants such as glutathione (GSH), α-tocopherol, ascorbic acid and ceruloplasmin were significantly altered when compared to controls, and the activities of antioxidant enzymes were remarkably elevated ($P<0.001$) in sprayer populations, when compared to controls. The important

difference between my study and that of ***Olga Lopez et al*** is that the Antioxidant levels were elevated. Similar findings are also report by other workers from India.

The genetic variation in the Paraoxonase (PON1) polymorphism may explain these differences.[35,36,37] This may explain the varying levels of various Antioxidant levels in the OPC poisoned patients. In this study the Antioxidant levels were measured in people with long term exposure to OPC compounds , hence the levels of superoxide dismutase (SOD) and Glutathione reductase (GR) were reduced as compared to my study where they were elevated.

6.4 Malonyl Dialdehyde (MDA) Levels

Malonyl aldehyde(MDA) levels were also measured. MDA levels are indicative of lipid peroxidation. The levels of MDA was 2.10 n.mol/ml +/- 0.65 SD in the OPC patients and 1.25 n.mol/ml +/- 0.08 SD in normal controls.

The levels were significantly elevated in the OPC patients. There was no statistically significant difference in the MDA values between the survivors and the patients who expired. There was no statistically significant difference in the MDA values from day 1 to day 5. This could

be probably due to the severe and prolonged oxidative stress due to OPC poisoning.

In a study ***Biomonitoring of organochlorines, glutathione, lipid peroxidation and cholinesterase activity among pesticide sprayers in mango orchards*** **by Vipul K. Singh et al [41],** assay of acetyl and butyrylcholinesterases (AChE, BChE respectively) was done as an indirect measurement of OP exposure and levels of Malonyl dealdehyde (MDA) and Glutathione (GSH) were estimated in blood samples to determine their impact on redox potential in 31 sprayers and compared with 18 controls. Significantly inhibited AChE, BChE activities and higher MDA level were found among sprayers compared to controls.

In this study MDA levels were found to be elevated, which is in concurrence with findings of my study, however the GSH levels were found to be low in this study in contrast to the findings of my study. This could be explained by the difference in the nature of poisoning. In my study, all the patients had acute poisoning in contrast to the chronic nature in the above study. The small sample of the study may also be contributory to the differences in the findings.

6.5 Plasma and RBC Cholinesterase levels

The Plasma Cholinesterase level was measured in the 50 OPC patients and 30 normal controls. The mean Pl. Ch. levels in the normal control was 175.40 microns/ml +/- 8.92 SD and it was 83.84 microns/ml +/- 10.58 SD in OPC poisoning patients. The Pl. Ch. levels was significantly reduced in OPC poisoned patients. There was however no statistically significant difference in the Pl.Ch.levels between the survivors and the patients who expired. The Plasma cholinesterases levels were reduced in my study as universally seen in all patients. The RBC Cholinesterase levels were reduced on Day 1 in both group of patients and they had increased on day 5 in both group of patients. The difference in the RBC Cholinesterase levels between the patients who improved and the patients who expired was not significant.

6.5. Co-relation analysis between POP score of the patient and the Anti-oxidant levels

There was co-relation between the POP score and the serum Anti-oxidant, MDA levels. The Antioxidant levels were elevated in all cases of OPC poisoning irrespective of the POP score. However the POP score was not predictive of the increase in the Antioxidant levels. This is due to the severe and prolonged oxidative stress produced by the OPC

compounds. Even small quantities of OPC compounds were capable of producing oxidative stress, however they may not produce markedly deranged clinical parameters. The POP score is a clinical score hence it has its own limitations in detecting biochemical derangements.

There was no variation in the POP score due to age, sex diffrerences among the victims. Similarly there was no difference in the Antioxidant levels in the patients which could be attributed to the sex of the patient, quantity of the OPC consumed. The treatment given did not influence the Antioxidant levels.

Pathophysiology of Oxidatve stress in patients with OPC poisoning

Free radicals are atoms or molecules containing one or more unpaired electrons: they are unstable and strive to restore parity. The oxygen—centered radicals which are produced under normal aerobic metabolism are also called reactive oxygen species (ROS); they are mainly produced by leukocytes and by the respiratory mitochondrial chain; they are essential for cell signaling, and for defense against infections. Another category of free radicals are derived from nitric oxide metabolism (NOS) and is the normal byproduct of endothelial metabolism.

Induction of reactive oxygen species by Organophosphorus Compounds and subsequent depletion of antioxidant cell defenses can result in disruption of the pro-oxidant / antioxidant balance in human tissues. The events following acute OPC provide a conducive setting for free radical generation [37-39,43,44,45].

The main cause of morbidity due to organophosphate poisoning is intermediate syndrome (Type II paralysis) that can occur 48-72 h after poisoning. In acute organophosphate poisoning, severe and prolonged

acetylcholinesterase inhibition is associated with oxidative stress, detected in erythrocyte membranes, that occurs early in the course of poisoning and may contribute to the development and severity of Intermediate syndrome. It may also be responsible for delayed Polyneuropathy. Free radicals mediate muscle damage and inflammation after strenuous exercise as well as the cellular injury of ischaemia-reperfusion as proposed by ***Dandapani et al [31], Lachance PA, Nakat Z, Jeong WS [43]*** .

Therefore the extensive muscle fasciculations and overactivity that occur in the cholinergic crisis of acute OPP and the paralysis following muscle overactivity which simulate ischaemia re-perfusion can both lead to free radical production and muscle damage. Studies in rats show that organophosphate induced muscle hyperactivity leads to free radical production with lipid peroxidation, a contributing factor to organophosphate induced cell injury.

Similar injury to the muscle may take place in acute OPC and contribute to the development of Intermediate syndrome. The source of free radicals in acute OPC is probably muscles. Oxidative damage of erythrocyte membrane lipid and protein may reflect similar reactions

occurring in the myocyte. Free radical damage to myocytes may contribute to the muscle weakness in acute OPC.

Recent work of **Yang *et al*** [39]show the inductionof heat shock protein 70 (HSP70) in cultured muscle cells exposed to dimethoate. Heat shock proteins are known to protect cells from oxidative stress and if induced in OPC patients may partly explain the low levels of oxidative stress observed in a few patients patients despite their severe poisoning .

A study by ***M. Dandapani, A. Zachariah, Oxidative damage in intermediate syndrome of acute organophosphorous poisoning***[31.] Showed that Oxidative stress was one of the major cause for the development of Intermediary syndrome.

Apart from these manifestations of OPC poisoning, according to ***TR Shobha et al*** [25] transient renal glycosuria has also been observed in patients with Organophosphate and Carbamate Poisoning. The proposed mechanism of action was probably due to Oxidative stress.

The acute and sub acute clinical manifestations of the Oxidative stress may be in the form of Respiratory distress, Intermediary syndrome, Delayed Polyneuropathy. These may be easily manifest in the POP score of the patients. However only a few patients develop these complications.

The proposed reasons include polymorphism of the Paroxanase 1 (PON 1) gene [39-41].

The long-term effects of the severe oxidative stress due to the OPC poisoning are yet to be elucidated. A few diseases which are attributed to be due to increased oxidative stress are [22,44] :

1. Accelerated aging
2. Acute pancreatitis
3. Allergies
4. Arthritis and other autoimmune diseases
5. Asthma
6. Atherosclerosis
7. Cancer
8. Diabetes, diabetic cataract
9. Drug toxicity
10. Emphysema
11. Neuronal stress (related to cognitive function)

12.Inflammatory bowel disease

13.Liver cirrhosis

14.Macular degeneration of the retina

15.Micronutrient deficiency

16.Osteoarthritis

17.Parkinson's disease and possibly Alzheimer's disease

18.Premature retinopathy

19.Reduced immune system function

20.Rheumatoid arthritis

21.Birth defects

22.Pre – Eclampsia/ Eclampsia

23.Endothelial dysfunction.

Many of the above mentioned diseases have well established etiological and genetic basis, however the oxidative stress may accelerate and aggravate the primary disease process.

Hence we need to follow up the patients with OPC poisoning for any of the above diseases.

A therapeutic strategy to increase the antioxidant capacity of cells may fortify the long term effective treatment. This may be accomplished by either reducing the possibility of toxicants interacting with critical bio-molecules and inducing oxidative damage, or by bolstering the cells, antioxidant defenses through endogenous supplementation of antioxidant molecules.

Although, many investigators confirmed induction of oxidative stress in many instances of diseases or following exposure to toxins, the usefulness of antioxidants alone or in conjunction with a drug has not been extensively investigated yet [53-54].

Antioxidants are substances, which inhibit or delay oxidation of a substrate while present in minute amounts. Endogenous antioxidants (AOX) defenses are both non—enzymatic (e.g. uric acid, glutathione, bilirubin, thiols, albumin, and nutritional factors, including vitamins and phenols) and enzymatic (e.g. the Superoxide Dismutases, Glutathione peroxidases, and Catalase). In the normal subject, the endogenous antioxidant defences balance the production of ROS, but for the average 1% daily leak, the most important source of Antioxidants is provided by

nutrition. These Antioxidants are not adequate to overcome the severe Oxidative stress brought by OPC Ingestion [43-48].

The patients in my study had received all the standard treatment protocols for OPC poisoning like Inj Atropine, Inj P_2 AM , Mechanical Ventilation, etc. However there was no difference in the Antioxidant levels between the patients who received these treatments and those who did not. This again re-emphasizes that the Oxidative stress occurs irrespective of the type of OPC, Quantity of OPC, Age of the patient, treatment received, etc. According to ***Stohs SJ: The role of free radicals in toxicity and disease*** [44] in considering Antioxidant therapy for patients with acute OPC poisoning it may be necessary to use multiple Antioxidant combination therapy instead of using a single compound as a single compound may cause imbalance in the oxidation-antioxidant cycle.

7. CONCLUSIONS

- The total Anti-oxidants were significantly elevated in patients with OPC Poisoning when compared to normal controls.

- Individual Anti-oxidants like Super oxide dismutase (SOD), Catalase, Malonyl dialdehyde (MDA), Glutathione Reductase, Glutathione transferase were significantly elevated in patients with OPC Poisonig when compared to normal controls

- The elevated antioxidant levels could not be attributed to the individual type of OPC compound.

- The elevated antioxidant levels could not be attributed to differences in sex, age, geographical location, treatment etc.

- There was no significant difference in the levels of Total Anti-oxidants between the patients who survived and the patients who died.

- There was no significant difference in the levels of Individual Anti-oxidants like Super oxide dismutase (SOD), Catalase, Malonyl diadehyde (MDA), Glutathione Reductase, Glutathione transferase between the patients who survived and the patients who died.

- There was no significant difference between the levels of Total Anti-oxidants on Day 1 and Day 5 in patients with OPC poisoning

- There was no significant difference between the levels of Individual Anti-oxidants like Super oxide dismutase (SOD), Catalase, Malonyl Aldehyde (MDA), Glutathione Reductase, Glutathione transferase on Day 1 and Day 5 in patients with OPC poisoning

- There was significant reduction the Plasma Cholinesterase levels of patients with OPC Poisoning when compared with normal individuals.

- There was significant reduction the RBC Cholinesterase levels of patients with OPC Poisoning when compared with normal individuals.

- There was minimal increase in the levels of Plasma Cholinesterase and RBC cholinesterase by Day 5.

- There was significant co-relation between the Peradeniya

  Organophosphorus Poisoning scale and the outcome, higher score indicating poor prognosis.

- The increase in the Total Anti-oxidant levels was occurring in all patients of OPC poisoning , without any co-relation to the Peradeniya Organophosphorus Poisoning scale (POP).

- The increase in Super oxide dismutase (SOD), Catalase, Malonyl dialdehyde (MDA), Glutathione Reductase, Glutathione transferase was occurring in all patients of OPC poisoning , without any co-relation to the Peradeniya organophosphorus scale (POP).

Limitations of the study

In India only one similar study has been done previously by ***Vidyasagar et al*** [21]. the findings of my study are in concurrence with that study, however in that study there was no attempt at co-relation between the clinical scenario and the anti-oxidant levels. However there were no other studies available for comparision from India, hence the results of this study need to be validated.

In my study the underlying Anti-oxidant status was not available, moreover many conditions like Chronic/occupational exposure to OPC compounds, Diabetes Mellitus , Coronary artery disease, Smoking , Alcoholism , Normal aging etc can alter the Anti-oxidant status.

All these conditions could not ruled out or taken into consideration due to lack of adequate history and clinical data, which may cause confounding of the data.

In my study I could not do a long term follow up on the Clinical status and the Anti-oxidant status of the patients as most of the patients admitted in our centre are referred from far away peripheral hospitals and follow up is difficult due to the distances involved

In my study I did not attempt intervention with Anti-oxidant supplements due to non-availability of safe and cheap agents.

In this study the controls could not matched accurately with respect to the patients as the patients admitted with OPC poisoning are usually admitted in an emergency condition with unpredictable and variable demographic, clinical and geographic profile.

8. THE ROAD AHEAD...

Conventionally the patients with OPC poisoning are treated with Inj Atropine, Inj P_2 AM , Mechanical Ventilation, etc. The deleterious effects of the Oxidative stress in these patients are usually not recognized and are ignored.

The Oxidative stress produced by the OPC compounds have demonstrated by various studies in this regard, however there has been no large multi-centric study on the clinical manifestations and implication of the OPC induced Oxidative stress. A few studies done in this regard have a small size and are not prospective studies. The need of the hour is to have large multi-centric long term prospective studies on the role of Oxidative stress in OPC poisoned patients.

The role of therapeutic intervention in the form of supplemental Antioxidants also needs to be explored. Hypothetically the patient may benefit from Anti-oxidant supplements along with standard treatment for OPC poisoning. Large studies are needed to explore this hypothesis and if found true, we may be able to predict and prevent the potentially fatal complication of Intermediary syndrome in OPC patients.

This may also be beneficial to people who have occupational exposure to OPC compounds like agricultural workers and people living in vicinity of agricultural farms . Since they are chronically exposed to low dose OPC compounds, they may not have any acute manifestation of OPC poisoning, however, they usually have chronic manifestations of OPC poisoning. This may be reduced to a certain extent by giving them regular Anti-oxidant supplements.

Legislative measures to reduce the burden of deaths due to OPC poisoning may include banning highly toxic OPC compounds like Monocrotophos, Folidol etc. They should be replaced with less toxic compounds like Pyrethroids.

The role of individual susceptibility to the harmful effects of OPC compounds due to genetic variations (PON 1 mutations) should be further studied as this may have therapeutic implications in individualizing the treatment of patients with either acute OPC poisoning or chronic OPC exposure. It may also be used as a tool in pre-employment screening in jobs which may involve occupational exposure to OPC compounds like agricultural sprayers etc.

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PROFORMA

Clinical and biochemical profile of patients with OPC poisoning

1. Name:
2. Age(yrs):
3. Sex: M / F
4. Address:
5. Occupation:
6. DOA: __/__/__
7. Duration of stay in hospital:
8. Outcome: Improved / Expired
9. OPC consumed:
10. Quantity (ml):
11. Route of exposure:
12. Time since exposure (mins):
13. Suicidal / Accidental / Occupational:
14. Treatment given outside: Yes / No :

Clinical features

Peradeniya organophosphate poisoning score

Parameter		score
Miosis		
	Pupils > 2mm	0
	Pupils ≤ 2mm	1
	Pupils pin-point	2
Fasciculation		
	None	0
	Present	1
	Generalized/ continuous & cyanosis	2
Respiration		
	≤ 20/ min	0
	> 20/ min	1
	> 20/ min & cyanosis.	2
Heart rate		
	> 60 /min	0
	41-60 /min	1
	≤40 /min	2
Level of consciousness		
	Conscious / alert	0
	Impaired, responds to verbal commands	1
	No response to verbal commands	2
	Convulsions	+1

Total score (Max score – 11)

POP score on Day 1: _____
Day 3: _____
Day 5: _____
Day 7: _____

Treatment given:

1) Atropine: _____
   a) Dose (mg/day):

   b) No of days:

2) P2AM :_____
   a) Dose (mg/day):

   b) No of days:

3) Others:
   a) **V**entilatory support: Yes___/No___

   b) No of days:

BIO-CHEMICAL INVESTIGATIONS
(Antioxidant Levels)

Sl no	Investigation	D 1	D 5
1)	Superoxide dismutase (micro.mol/gmHb %)		
2)	Catalase (micro mol/ gm Hb%)		
3)	Glutathione reductase (mcg/ gm Hb%)		
4)	Glutatione peroxidase (mcg/ gm Hb%)		
5)	MDA (n.mol/ml)		
6)	Glutathione Transferase (n.mol/gmHb%)		
7)	Total antioxidants (m.mol / L)		
8)	RBC Cholinesterase (mcg/ ml)		
9)	Plasma Cholinesterase (mcg/ ml)		

AGE(Yrs)	SEX	OCC	LOCALITY	DUR_HOS (Days)	Type of Po	Route of Exposure	Quantity ml	Time of onset (Mins)
30	1	1	2	2	FOLIDOL	INGESTI	60	45
32	1	1	1	7	CHLORPY	INGESTI	50	45
25	1	3	2	7	HINOXAN	INHALAT	15	30
23	1	2	1	7	MONOCR	TOPICAL	50	45
30	2	1	2	3	PHORATE	INGESTI	5	60
55	1	1	1	6	DIMECRO	INHALAT	25	120
38	1	1	1	12	DIMECRO	INHALAT	265	40
38	1	1	2	15	DIMECRO	INGESTI	250	30
23	1	2	1	8	FOLIDOL	INGESTI	50	45
20	2	3	2	14	CHLORPY	INGESTI	75	40
24	1	2	1	6	TRIPHOS	INGESTI	50	30
40	1	2	2	4	FOLIDOL	INGESTI	50	30
32	1	3	2	6	EKALUX	INGESTI	60	60
35	1	1	1	6	FOLIDOL	INGESTI	125	20
45	1	3	1	22	DIMETHO	INGESTI	220	15
40	1	1	1	6	FOLIDOL	INGESTI	440	35
25	1	1	1	5	DIMECRO	INGESTI	70	30
42	1	2	2	6	FOLIDOL	INGESTI	60	45
21	1	2	2	7	TRIPHOS	INGESTI	234	30
54	1	2	1	3	PARATHIO	INGESTI	50	30
8	1	2	2	5	DIMECRO	INGESTI	200	15
26	1	2	2	6	EKATOX	INGESTI	145	60
20	1	2	1	6	FOLIDOL	INGESTI	100	20
20	1	1	1	7	DIMECRO	INGESTI	100	50
46	1	2	2	5	FOLIDOL	INGESTI	65	30
18	1	3	1	9	PARATHIO	INGESTI	50	30
25	1	1	2	13	DIMECRO	INGESTI	350	20
14	1	2	2	5	CHLORPY	INGESTI	40	45
22	1	1	2	5	DIMECRO	INGESTI	90	75
50	1	1	2	5	FOLIDOL	INHALAT	10	20
23	1	1	2	14	PARATHIO	INGESTI	57	60
27	2	1	1	5	FOLIDOL	INGESTI	66	45
23	1	2	2	7	DIMECRO	INGESTI	25	55
50	1	1	2	5	FOLIDOL	INHALAT	5	20
32	1	1	2	3	METAPHO	INGESTI	60	60
28	1	1	1	11	DIMETHO	INGESTI	30	45
26	1	2	2	6	DIMECRO	INGESTI	36	60
18	2	2	1	5	DIMECRO	INGESTI	40	20
20	1	1	2	5	TRIPHOS	INGESTI	45	90
20	1	2	1	5	EKALUX	INGESTI	45	60
17	2	2	2	6	FOLIDOL	INGESTI	15	30
23	1	1	2	6	DIMETHO	TOPICAL	100	50
54	1	2	1	3	PARATHIO	INGESTI	175	30
32	1	1	1	7	CHLORPY	INGESTI	50	45
24	1	2	2	5	HINOXAN	INHALAT	10	15
21	1	1	2	6	PHORATE	INGESTI	76	120
46	1	2	2	5	FOLIDOL	INGESTI	90	30

32	1	3	2	6	FOLIDOL	INGESTI	80	60
45	1	3	1	22	BAYTEX	INGESTI	145	15
22	1	2	1	5	FOLIDOL	INGESTIO	70	30

Intention	Time of first aid (Hrs)	POP Day 1	POP Day 3	POP Day 5	Total Antioxidants D 1	Total Antioxidants D 5	SOD D 1	SOD D 5
1	1.50	5	5	2	1.05	1.44	6.63	6.84
1	2.00	5	4	2	0.96	1.91	6.16	6.86
2	6.00	7	5	3	0.96	1.86	7.12	6.16
2	15.00	5	5	3	0.91	2.05	8.05	6.04
1	1.00	6	6	4	0.84	1.99	8.44	5.34
2	1.00	9	9	7	0.91	1.19	8.10	7.12
2	1.00	10	8	7	0.99	0.92	7.92	6.34
1	.50	10	10	6	0.88	0.81	8.10	5.92
1	2.00	6	4	2	0.79	2.21	8.14	6.92
1	1.00	7	7	5	0.84	1.27	6.34	6.16
1	2.00	1	1	5	1.10	1.34	8.54	7.54
1	1.00	6	5	4	0.88	2.28	8.12	6.96
1	2.00	4	3	3	0.82	2.44	9.84	7.54
1	1.00	8	8	5	0.71	1.36	7.12	6.04
1	.50	10	9	6	0.88	0.96	6.92	7.12
1	6.00	10	8	7	0.92	1.05	6.16	6.04
1	2.00	5	6	5	1.03	1.42	6.64	6.73
1	1.00	5	5	4	0.86	2.47	9.82	7.59
1	.75	7	4	5	0.92	1.31	8.06	7.02
1	2.00	6	8	7	1.14	1.26	8.10	6.12
1	3.00	10	9	9	0.99	1.08	7.05	6.34
1	4.00	7	6	3	0.96	1.92	8.02	6.08
1	.50	8	6	7	0.96	1.38	7.12	6.32
1	2.00	5	7	6	0.93	1.89	6.12	6.83
1	1.00	7	4	3	0.92	1.88	7.10	6.22
1	2.00	4	3	3	0.96	2.05	8.12	6.02
1	2.00	10	8	8	0.96	1.10	6.84	7.12
1	2.00	9	9	8	0.84	1.16	8.54	7.12
1	2.00	8	6	5	0.90	1.22	7.18	6.29
2	.75	3	3	3	1.10	1.36	8.56	7.43
1	2.00	5	6	3	0.91	1.90	6.15	6.80
1	1.00	8	6	5	1.26	1.26	8.05	6.12
1	1.00	3	3	3	0.90	1.92	6.11	6.87
2	.75	3	3	2	0.92	1.88	7.10	6.25
1	3.00	6	6	8	0.96	2.05	8.12	6.05
1	8.00	4	6	4	0.91	2.01	8.17	6.10
1	4.00	6	6	3	0.92	2.12	7.22	6.08
1	2.00	5	4	3	0.97	1.92	6.20	6.86
1	2.00	7	7	8	0.90	1.24	7.22	6.28
1	2.00	4	3	2	0.88	2.42	9.88	7.57
1	3.00	4	3	3	1.20	1.48	8.22	7.60
2	20.00	4	7	4	0.82	2.42	9.82	7.54
1	2.00	9	8	8	1.08	1.16	6.16	6.14
1	2.00	4	7	6	0.96	1.90	6.14	6.84
2	6.00	5	7	4	0.92	1.88	7.02	6.18
1	4.00	6	4	4	0.92	1.88	6.22	6.82
1	1.00	8	7	6	0.91	1.20	7.16	6.26

1	2.00	7	6	5	0.96	1.82	7.02	6.18
1	.50	4	7	5	1.08	1.48	6.66	6.80
1	2.00	6	5	5	1.00	1.90	6.19	6.88

MDA D 1	MDA D 5	CATALASE D 1	CATALASE D5	Glutathione Reductase D 1	Glutathione Reductase D 5	Glutathione Transferase D 1	Glutathione Transferase D 5	RBC Cholinesterase D 1
1.84	1.72	5.53	5.16	10.80	9.81	5.83	4.93	161
2.16	2.06	4.06	3.54	13.60	9.20	6.84	5.08	138
1.84	1.82	6.10	3.92	11.40	9.18	5.92	5.59	152
1.38	1.58	6.16	4.16	9.80	9.12	6.84	5.15	132
1.36	1.54	5.54	4.41	11.60	9.54	6.68	5.26	158
2.10	2.16	5.16	4.05	10.20	9.26	6.41	5.19	151
2.31	2.03	5.92	3.84	11.60	9.61	6.91	4.92	141
1.91	1.94	6.62	4.05	10.80	8.86	6.16	5.36	154
2.82	2.71	5.01	4.16	11.20	10.80	4.98	4.91	158
1.28	1.44	4.41	4.48	11.40	10.20	6.32	5.38	39
3.84	3.14	5.15	4.41	10.20	8.96	5.96	5.11	140
1.96	1.94	5.92	5.03	11.70	9.05	5.76	6.02	154
1.64	1.83	6.38	5.02	9.84	8.12	5.43	5.13	152
1.92	1.76	6.34	4.49	12.20	9.60	4.96	4.84	156
1.91	1.84	4.03	3.12	9.80	9.12	5.08	5.01	141
2.83	2.64	5.54	4.16	10.10	9.34	5.62	4.26	146
1.90	1.71	5.55	5.19	10.82	9.87	5.81	4.95	163
1.52	1.82	6.45	5.09	9.89	8.10	5.44	5.17	150
2.61	2.07	5.54	3.39	12.20	9.13	5.81	5.08	148
3.23	3.12	5.90	3.90	10.62	9.22	4.57	6.00	122
2.05	2.03	5.32	4.32	10.80	8.16	6.36	6.02	154
1.40	1.51	6.18	4.17	9.82	9.10	6.86	5.18	140
2.62	2,04	5.84	5.38	10.90	9.96	5.92	4.44	164
2.16	2.06	4.06	3.52	13.53	9.22	6.84	5.02	133
1.81	1.85	6.12	3.95	11.41	9.13	5.88	5.60	150
1.38	1.53	6.12	4.17	9.80	9.11	6.86	5.15	134
3.36	3.12	6.05	4.38	8.89	7.14	5.02	4.92	136
0.98	1.10	5.96	4.48	9.89	9.12	5.84	4.34	138
2.04	1.00	6.11	5.18	9.60	8.60	5.90	5.11	141
3.84	3.20	5.19	4.45	10.20	8.96	5.83	5.09	145
2.10	2.09	4.06	3.50	13.50	9.27	6.88	5.05	131
3.18	3.02	5.86	3.96	10.60	9.24	4.61	6.01	126
2.14	2.04	4.11	3.50	13.56	9.24	6.84	5.00	129
1.92	1.78	6.18	4.02	11.41	9.18	5.90	5.60	154
1.42	1.61	6.21	4.17	9.85	9.32	6.79	5.24	148
1.34	1.53	6.14	4.17	9.72	9.18	6.83	5.20	141
1.48	1.86	6.32	4.23	9.34	9.26	6.66	4.94	156
2.20	2.12	4.02	3.50	13.26	9.26	6.80	5.12	138
2.14	1.15	6.20	5.18	9.64	8.54	5.72	5.12	148
1.61	1.88	6.40	5.08	9.88	8.17	5.47	5.20	162
3.22	3.40	5.22	4.40	10.12	8.40	5.76	5.14	147
1.62	1.88	6.40	5.08	9.81	8.18	5.44	5.13	150
1.66	1.64	5.32	4.12	11.20	8.82	5.08	5.91	138
2.20	1.98	4.16	3.46	13.50	9.28	6.74	5.12	134
1.98	1.84	6.22	4.12	11.44	9.08	5.86	5.48	160
2.22	2.14	4.10	3.52	13.12	9.22	6.82	5.18	140
84.00	1.05	6.16	5.16	9.61	8.61	5.91	5.08	144

1.88	1.86	6.12	3.94	11.40	9.20	5.92	5.62	150
1.88	1.73	5.50	5.20	10.60	9.76	5.72	4.92	160
2.18	2.10	4.10	3.55	13.62	9.22	6.88	5.12	140

RBC Cholinesterase D 5	Pl Cholinesterase D1	Pl Cholinesterase D 5	Ventilatory support	Outcome
310	78	128	1	1
191	51	131	1	1
191	61	121	2	1
172	58	98	1	1
184	44	124	1	1
276	48	137	2	2
272	74	136	2	2
184	66	110	2	2
210	56	196	1	1
217	55	126	2	1
259	71	128	1	1
296	91	150	1	1
282	61	110	1	1
205	54	104	2	2
276	60	141	2	2
191	51	128	2	2
302	78	130	1	1
286	63	115	1	1
183	88	108	1	1
182	80	145	1	1
301	55	131	2	2
179	60	100	1	1
271	54	134	2	2
190	55	133	1	1
193	63	121	1	1
174	57	99	1	1
251	54	192	2	2
196	64	132	2	2
180	68	150	2	1
250	80	130	1	1
200	51	134	1	1
184	78	146	2	1
201	55	133	1	1
190	68	128	1	1
172	60	102	1	1
179	57	106	1	1
184	62	110	1	1
192	58	133	1	1
180	72	140	2	1
282	70	116	1	1
246	82	132	1	1
287	65	114	2	1
192	61	121	2	2
194	62	136	1	2
188	66	120	1	1
198	60	132	1	1
176	68	148	2	2

196	64	122	2	1
312	80	124	1	1
190	55	124	1	1