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Comparison of the Safety and Efficacy of Atropine, Pralidoxime With or Without Magnesium Sulphate in the Management of Inhaled and Ingestional Organophosphate Poisoning

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ABSTRACT: The main Concept is compare the safety and efficacy of Atropine, Pralidoxime, Magnesium Sulphate in Organophosphate poisoning.The main objective is to compare the efficacy of Atropine, Pralidoxime, and Magnesium Sulphate in Organophosphate poisoning.To assess Severity of poisoning by using Peradeniya Organ phosphorus poisoning Scale (POP Scale).To study the adverse drug reactions of Atropine, Pralidoxime, Magnesium Sulphate in Organophosphate poisoning. This study needs to dose management of Atropine, Pralidoxime, Magnesium Sulphate regarding severity of Organophosphate poisoning, to Reduce Mortality rate in Organophosphate poisoning and to Reduce Hospital stay, Treatment duration associated with Organophosphate poisoning.

I. INTRODUCTION

Organ phosphorus compounds are widely employed as pesticides not only in agriculture and horticulture, but also in households to combat vector-borne diseases such as malaria and dengue. OP (Organo Phosphorous) compounds and carbamates are two types of pesticides that inhibit the AChE (Acetyl Cholinesterase) enzyme and cause human toxicity. The Cleemont group created the first OP, tetraethyl pyrophosphate, in 1854.

TYPES OF OP COMPOUNDS

There are many types of organ phosphorous compounds which are used commonly. These are classified on the basis of their toxicity, use, chemical structure.

Based on toxicity:
Highly Toxic Op – mainly for agricultural use.Eg: tetra ethyl pyrophosphate, parathion.
Intermediate Op – mainly for animal use Eg: coumaphos, chlorpyrifos, trichlorfon.
Low Toxic Op- household application and as field sprays.Eg: diazonin, malathion,dichlorvos .
Based on use of OP compounds:
Insecticides: Parathion, Diazinon, Dichloruos ,Chloropyrifos, Malathion , Tenthion, Ethion, Profenofos , Monocrotophos .
Nerve Gases: Soman ,Sauin ,Tabun.
Ophthalmic Agents: Echothiophate ,Isoflurophate.
Herbicide: Merphos ,Tributos.
Antihelmintics : Trichlorofon.

Based on Chemical Structure :
Aryl Phosphates:
Parathion, Paraoxon, Methylparathion, Diazoin.
Alkyl Phosphates: Tetra ethyl pyrophosphate, Profenofos, Malathion, Octamethyl.
Pyrophosphamide,: Sulfotepp, Demeton, Fenthion.

Toxic kinetics Of Op Compound Poisoning:
Absorption: As these compounds are highly lipid soluble, hence they are easily absorbed from intact skin, oral mucus membranes, conjunctiva, gastrointestinal and respiratory tracts.
Distribution: Organ phosphorous compounds rapidly distributes to all parts ; highest concentration is seen in liver and kidney. Also they can easily pass through blood brain barrier.
Metabolism: occurs in liver, by the Cytochrome P450 enzymes &process of Oxidation, hydrolysis, conjugation. Half life is from minutes to hours.
Elimination:organophosphorous compounds and metabolites eliminates through urine, bile & faeces27.

Mechanism Of Op Compound Poisoning

Acetylcholine is a chief neurotransmitter which is found in CNS and PNS neurotransmitter junctions, RBCs, sweat glands. Acetylcholine is synthesized in nerve terminals from acetyl co enzyme and choline ,this reaction is catalysed by choline acetyl transferase (CAT) .Ache decreases

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accumulation of Ach is nerve terminals (or)synapses. It has a catalytic activity (high).

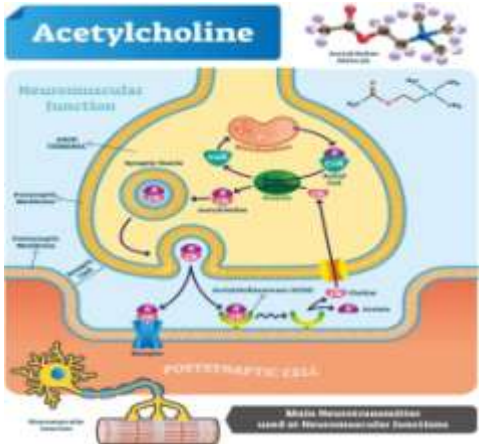

Fig :Mechanism Of Acetyl Choline

Acetylcholine acts on 2 types of receptors

Muscarinic receptors-

- M1- cortex , salivary, gastric.
- M2 - Smooth muscle, cardiac tissue.
- M3 – Bronchioles, Iris, bladder.
- M4, M5 – Hippocampus, substantianigra, other locations of brain

Nicotinic receptors are:-

- NN- Adrenal Medulla, Autonomic ganglia, CNS.
- Nm – Neuromuscular Junction.

Clinical presentation of OP poisoning:-

These symptoms occur due to the inhibition of Ache which leads to excess of Acetylcholine act CNS, autonomic nervous system. This leads to overstimulation of Muscarinic and Nicotinic receptors. The severity of symptoms depends on type, quantity of consumption of OP compound.The symptoms are classified into

Muscarinic effects

- Cardiovascular

i) Bradycardia
ii) Hypotension

- Respiratory

i. Bronchorrhoea
ii. Bronchospasm
iii.Rhinorrhoea

- Gastro intestinal

i. Diarrhea
iiSalivation
iii.Abdominal pain
iv.Vomiting

- Eyes

i.Lacrimation
ii.Blurred vision

- Nicotinic effects

•Fasciculations
•Tachycardia
•Cramps
•Hypertension
•Paralysis
•Weakness

CNS effects

These occur due to overstimulation of Muscarinic receptors and nicotinic receptors.
•Anxiety
•Convulsions
•Coma
•Ataxia
•Restlessness
•Dysarthria.
•Tremors.
•Insomnia.
•Circulatory collapse.
•Respiratory depression.
.•Death

Complications:

3 well defined clinical phases are

- Initial acute Cholinergic crisis
- Intermediate syndrome
- OPIDN

1.Initial acute Cholinergic crisis :-

As OP compounds are inhibition of esterase i.e. Ache leading to AC C in initial phase. Muscarinic symptoms:--

- Diarrhoea
- Lacrimation
- Salivation
- Bronchorrhea
- Bronchospasm
- Bradycardia
- Urination
- Miosis

Nonetheless, the patient may experience hypertension & tachycardia rather than hypotension and bracycardia as a result of nicotinic actions depending on balance between nicotinic and muscarinic effects. Muscle paralysis results from acute intoxications activation of nicotinic receptors. Fasciculation may be seen.

Due to CNS effects, extreme intoxication may result in emotional irritation, mental

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obtundation, cognitive impairment, coma, convulsions. After exposure to these substances, complete clinical recovery from all symptoms may take up to a week. Paralysis often resolves during the cholinergic phase within 48-72 hrs.

2.Intermediate Syndrome :-

This discovery was initially referred to as Type-II paralysis by wadia et al, However senanayake&Karalliedde first used the phrase

"intermediate syndrome" refers to the condition that occurs between early cholinergic crisis & late onset of peripheral neuropathy. Its prevalence has been estimated to range from 20 to 68% in various studies. It has been established that substances like diazonin, dimethoate, methyl parathion, methamidaphos, monocryptopluspenthion, ethyl parathion are frequently linked to illness- muscular weakening in the ocular, neck, bulbar, proximal limb & respiratory muscles appear between 12- 96 hrs after exposure, reflecting a sustained action of acetyl choline on nicotinic receptors, sometimes dystonic posture& respiratory muscle weakness can be seen.

3.Organophosphate induced delayed polyneuropaths (OPIDN):-

OPIDN is common after exposure to OPCS with weak anticholinsterase activity, such as tiorthocresylphosphate. However it is extremely rare after exposure to currently available OPCS with strong anticholinsterase activity.

OPIDN develops after 7-21 days of exposure & causes significant morbidity.

Paresthesia and calf pain are first symptoms to appear. Weakness appear first in distal key muscles, causing foot drop & then into small muscles of hands. Later it may spread to the buccal muscles. It has sub acute onset and a slow progression over 2 weeks.

Follow up studies on people who have been exposed to high levels of organophosphorous compounds have revealed that they may develop certain neurobehavioral changes known as COPIND. Drowsiness, confusion, lethargy, anxiety, emotional liability, depression, fatigue and irritatability are among the side effect.

Some of these symptoms on the other hand could be attributed to the sequel of convulsions, anoxia, respiratory failure and cardiac arrhythmias that these patients experienced during the acute cholinergic syndromes like,

- Anxiety
- Depression
- Memory
- Concentration problems
- other chronic neuropsychiatric disorders.

During recovery from the cholinergic syndrome ,psychosis, delirium, aggression, hallucination and depression may occur.Other types of delayed neurobehavioral effects have been observed in people who have been exposed to low doses of organophosphorous compounds for extended periods of time.

MANAGEMENT :-

- Resuscitation
- Atropinization
- Benzodiazipines
- Oximes
- MgSO4
- clonidine

RESUSCITATION:

Resuscitation should continue as follows.

- Airway: Left lateral location of the airway
- Breathing: Check oxygen and start high flow oxygen or intubate if there is a sign of tachypnea or bradypnea
- Circulation: Check for evidence of poor perfusion in the circulation. Begin an IV infusion of 0.9% NS.For example, chilly, damp extremities and diaphoresis.
- Disability: Check your state of consciousness and your blood sugar levels.
- Examine: Assess SpO2, heart rate, pupil size, blood pressure, and chest sounds.

II. METHODOLOGY

Study Design: The present study is prospective observational study.

Study period: The study is conducted over a period of 6 months.

Study site: Govt. General Hospital, KURNOOL.

Source of data: Data will be collected from the patients who are admitted in teritary care hospital for the treatment of organophosphate poisoning who are prescribed with atropine, pralidoxime, magnesium sulphate.

INCLUSION CRITERIA:

- All the patients of either sex aged above 15yrs are included.
- All the patients of either sex consumed or exposed with organophosphate poisoning.
- All the patients who are willing to participate in the study are included.
- All the patients with comorbidities are also included.

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EXCLUSION CRITERIA:

- Pregnant women are excluded.
- Paediatric patients are excluded.
- Patients of either sex below 15yrs are excluded.
- Psychiatric and unco-operative patients are not included.
- Patients with doubtful history of poisoning with unknown compound are excluded.

Method of data collection:

- Patient demographic details proforma.
- Severity of poisoning by using PeradeniyaOrganophosphorus poisoning scale (POP).
- Data collection would be done by using patient demographic details proformas and Naranjo's scale proforma.

Statistical analysis:

- For further results the statistical analysis will be done.

III. RESULTS

Gender Wise Distribution:

A total of 105 subjects are presented with organophosphate poisoning in which we involved 58 cases for our comparisonstudy , in which 34 subjects are males and 24 subjects are females.

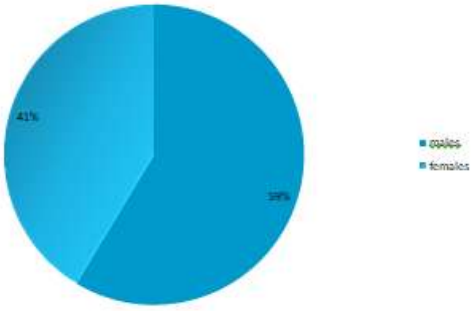

Fig :Gender wise distribution

Age wise distribution of patients

Age group between 14-24 are more prone to consumption of organophosphate poisoning.

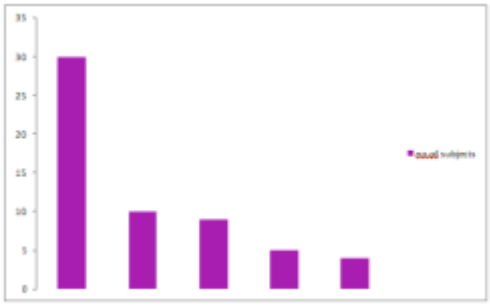

Fig: Age wise distribution

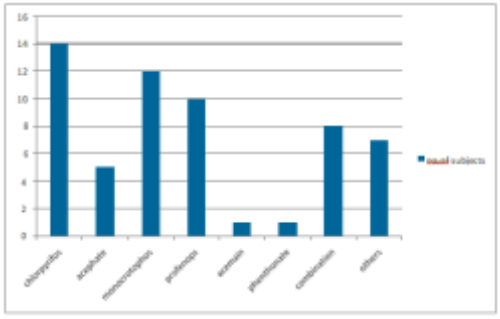

Fig : Distribution of patients according to the type of OP compound

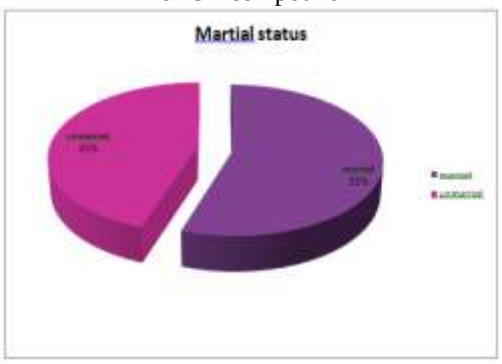

Fig :Martial status

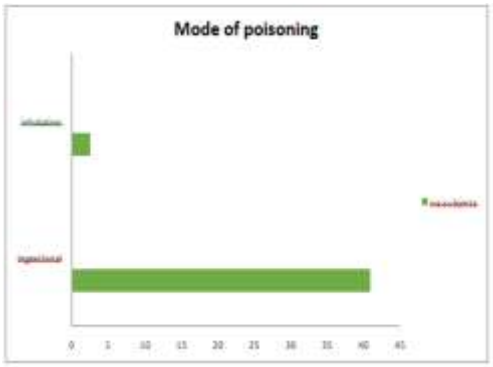

Fig:Mode of poisoning

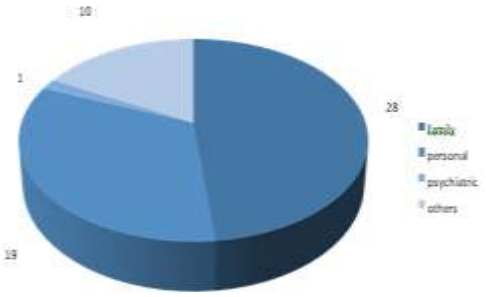

Fig:Reason for Poisoning

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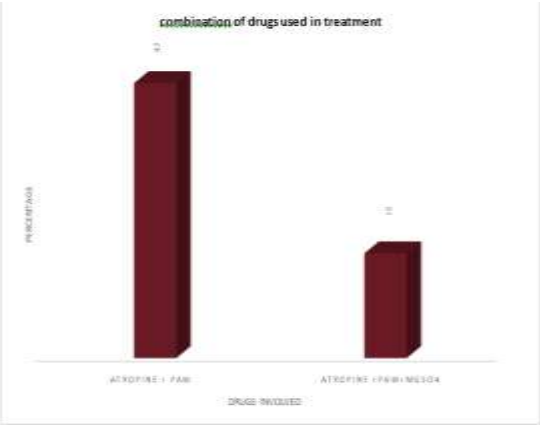

Fig :Combination of drugs used in treatment

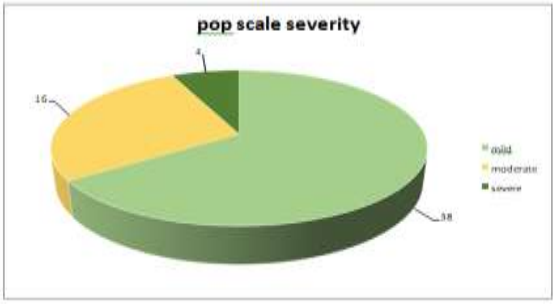

Fig: Severity Based On Pop Scale

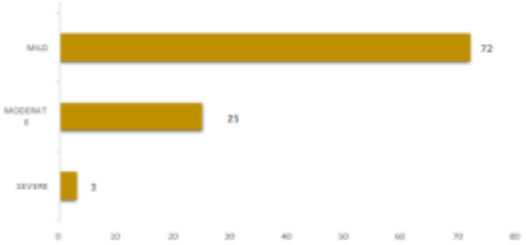

Fig: Treatment involving MgSO4

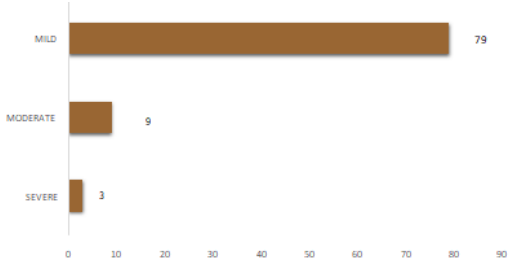

Fig: Treatment without involving MgSO4

Based on POP scale,Measurement of efficacy involving MgSO4 in their treatment along with atropine,PAM.

- Efficacy is measured by ICU stay, ventilation support, hospital stay and death as shown in table no 10
- Out of 21 subjects who are hospitalized due to mild exposure ICU stay is seen in 12(57%) subjects, ventilation support is needed in 11(52%) subjects, hospital stay more than 7 days is seen in 4(19%) subjects and there are 0(0%) deaths observed.
- Out of 07 subjects who are hospitalized due to moderate exposure ,ICU stay is seen in 06(86%) subjects, ventilation support is needed in 06(86%) subjects, hospital stay more than 7 days is seen in 7(100%) subjects and there are 0(0%) deaths observed.
- Out of 01 subjects who are hospitalized due to severe exposure ICU stay is seen in 01subjects, ventilation support is needed in 01 subjects, hospital stay less than or equal to 7 days is seen in 0 subjects and there are 1 death observed.

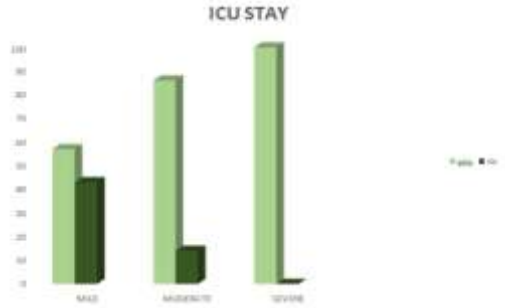

Fig: Based on POP scale,Measurement of ICU stay in subjects involving MgSO4 in their treatment along with atropine, PAM.

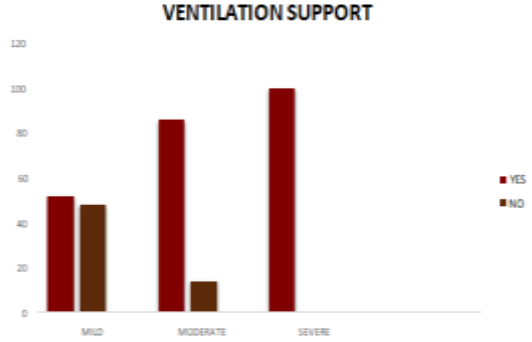

Fig : Based on POP scale, Measurement of ventilation support in subjects involving MgSO4 in their treatment along with atropine, PAM

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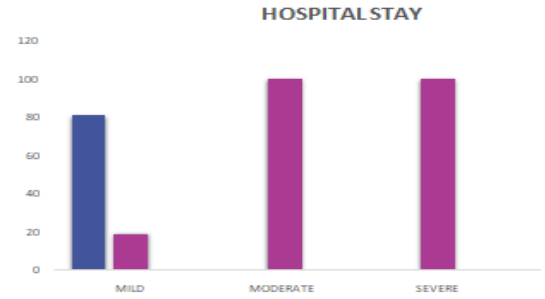

Fig: Based on POP scale, Measurement of hospital stay in subjects involving MgSO4 in their treatment along with atropine, PAM

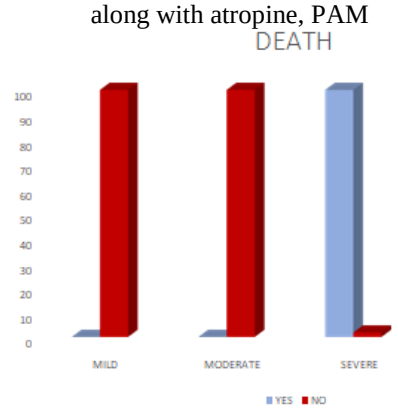

Fig :Based on POP scale, Measurement of death in subjects involving MgSO4 in their treatment along with atropine, PAM

Based on POP scale, Measurement of efficacy in subjects involving atropine,PAM.in their treatment alone.

- Efficacy is measured by ICU stay, ventilation support, hospital stay and death as shown in table no 11.
- Out of 17 subjects who are hospitalized due to mild exposure ICU stay is seen in 12(71%) subjects, ventilation support is needed in 07(41%) subjects, hospital stay more than 7 days is seen in 5(29%) subjects and there are 0 deaths observed.
- Out of 09 subjects who are hospitalized due to moderate exposure , ICU stay is seen in 07(78%) subjects, ventilation support is needed in 08(89%) subjects, hospital stay more than 7 days is seen in 9(100%) subjects and there are 1(11%) deaths observed.
- Out of 3 subjects who are hospitalized due to severe exposure ICU stay is seen in 3(100%)subjects, ventilation support is needed in 3(100%) subjects, hospital stay more to 7 days is seen in 1(33%) subjects and there are 1(33%) death observed.

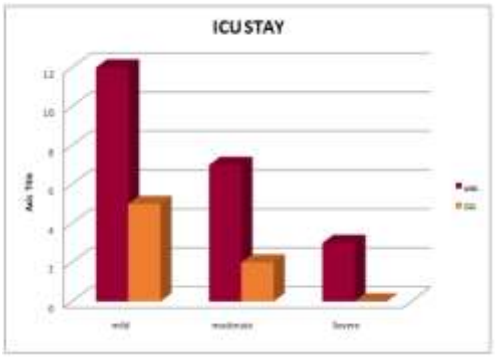

Fig: Based on POP scale, Measurement of ICU stayin subjects involving atropine, PAM in their treatment alone

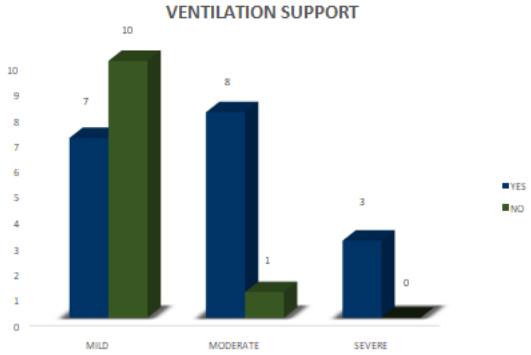

Fig: Based on POP scale, Measurement of ventilation support in subjects involving atropine, PAM in their treatment alone

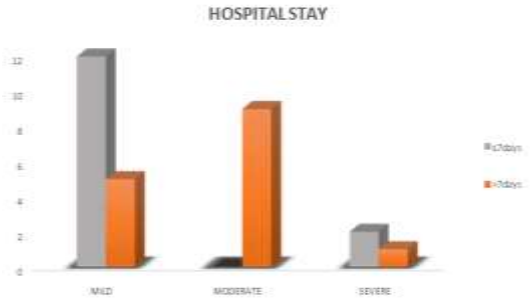

Fig : Based on POP scale, Measurement of hospital stay in subjects involving atropine, PAM in their treatment alone

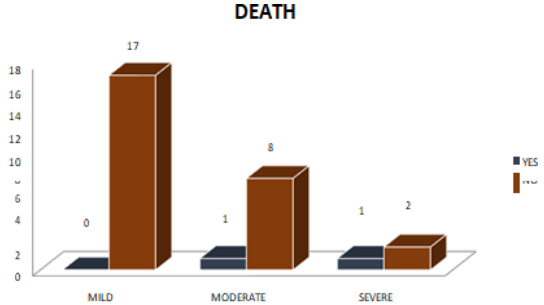

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Fig: Based on POP scale, Measurement of death in subjects involving atropine, PAM in their treatment alone.

Tests for normal distribution of ATROPINE + PAM + MgSO4 Hospital Stay:

Table: Tests For Normal Distribution Of ATROPINE + PAM + Mgso4 Hospital Stay

	Statistics	p
Kolmogorov-Smirnov	0.21	0.13
Kolmogorov-Smirnov (Lilliefors Corr.)	0.21	0.002
Shapiro-Wilk	0.94	0.091
Anderson-Darling	0.93	0.019

T-Test for independent samples

Table: Hypotheses

Null hypothesis	**Alternative hypothesis**
There is no difference between the ATROPINE + PAM + MgSO4 Hospital Stay and ATROPINE + PAM Hospital stay groups with respect to the dependent variable	There is a difference between the ATROPINE + PAM + MgSO4 Hospital Stay and ATROPINE + PAM Hospital stay groups with respect to the dependent variable

Descriptive statistics:

Table :Descriptive statistics

	N	Mean	Std. Deviation	Std. Error Mean
ATROPINE + PAM + MgSO4 Hospital Stay	29	6.41	1.43	0.27
ATROPINE + PAM Hospital stay	29	7.03	1.72	0.32

Table: t-Test for independent samples

	t	df	p (2-tailed)
Equal variances	-1.49	56	0.141
Unequal variances	-1.49	54.14	0.141

Table: 95% Confidence Interval of the Difference

	Mean Difference	Standard Error of Difference	Lower limit	Upper limit
Equal variances	-0.62	0.42	-1.45	0.21
Unequal variances	-0.62	0.42	-1.45	0.21

MEASUREMENT OF SAFETY:

Table: Adverse Drug Reactions Due To Atropine

ADR	**No.Of Subjects**
Psychosis	67
Breathlessness	32
Headache	10
Salivation	6
Fever	8
Seizures	2
None	22

Table: adverse drug reactions due to Pralidoxime

ADR	No.Of Subjects
Hypersensitivity reaction	1

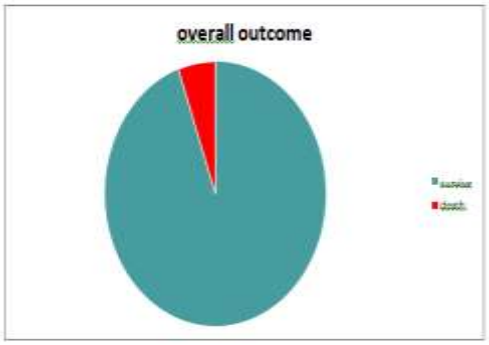

Fig : overall outcome

IV. DISCUSSION

In our study 105 patients are presented with organophosphate poisoning, we included 58 subjects for the comparative study to study efficacy, where males are more constituting 59% i.e. 34 male patients, and females constituted 41% i.e. 24 patients. Fatemahsamshidi.etal study represents 62.5% males and 15 (37.5%)

In this present study we found that most of op compound consumption is seen in age between 12-24 (58%) whereas in K.V.Ramanath. etal study major victims are belonged to age group between 21 to 40 years. In our present study, the most commonly ingested organophosphorus compound is chloropyrifos 14 (24%) , followed by

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monocrotophos 12(20%) and acephate 05 (8%) In this prospective observational study, intentional poisoning is seen in 41 (71%) subjects followed by accident or inhalational poisoning 17 (29%). In our present study, we found that major factor that contribute for organophosphate suicidal or intentional poisoning is family problems 28 (48%) followed by personal problems 19(32%) and psychiatric 1 (3%).

In our present study atropine, pralidoxime and MgSO4 i.e. 3 regimens are given in 29 (50%) subjects whereas atropine ,pralidoxime alone i.e. 20 regimens are given in 29 (50%) subjects. In our present study Peradeniya organophosphate poisoning scale (pop scale) is used to measure severity; among which mild 38 (66%), moderate 16(27%) and severe 4 (7%) are observed. In this prospective comparitive study the group of subjects in which 3 regimens are involved the efficacy is measured by based on 4 factors i.e. ICU stay, ventilation support, hospital stay and death based on pop scale severity as shown in table no 10.

Out of 21 subjects who are hospitalized due to mild exposure ICU stay is seen in 12(57%) subjects, ventilation support is needed in 11(52%) subjects, hospital stay more than 7 days is seen in 4(19%) subjects and there are 0(0%) deaths observed. Out of 07 subjects who are hospitalized due to moderate exposure ,ICU stay is seen in 06(86%) subjects, ventilation support is needed in 06(86%) subjects, hospital stay more than 7 days is seen in 7(100%) subjects and there are 0(0%) deaths observed.

Out of 01 subjects who are hospitalized due to severe exposure ICU stay is seen in 01subjects, ventilation support is needed in 01 subjects, hospital stay less than or equal to 7 days is seen in 0 subjects and there are 1 death observed. We can observe similar results in Banerjee etal study in which measurement of efficacy based on 4 factors. In this comparitive study the group of subjects in which 2 regimens are involved i.e. atropine and pralidoxime alone, the efficacy is measured based on pop-scale severity and 4 factors i.e. ICU stay, ventilation support, hospital stay and deaths as shown in table no.11. Out of 17 subjects who are hospitalized due to mild exposure ICU stay is seen in 12(71%) subjects, ventilation support is needed in 07(41%) subjects, hospital stay more than 7 days is seen in 5(29%) subjects and there are 0 deaths observed.

Out of 09 subjects who are hospitalized due to moderate exposure , ICU stay is seen in 07(78%) subjects, ventilation support is needed in 08(89%) subjects, hospital stay more than 7 days is seen in 9(100%) subjects and there are 1(11%) deaths observed.Out of 3 subjects who are hospitalized due to severe exposure ICU stay is seen in 3(100%)subjects, ventilation support is needed in 3(100%) subjects, hospital stay more to 7 days is seen in 1(33%) subjects and there are 1(33%) death observed. We can observe similar results in Banerjee etal study in which measurement of efficacy based on 4 factors.

In this study we analysed efficacy by using T –Test. The probability of the T-Test proves null hypothesis as there is no difference between There is no difference between the ATROPINE + PAM + MgSO4 Hospital Stay and ATROPINE + PAM Hospital stay groups with respect to the dependent variable

V. CONCLUSION

The present study compared that effectiveness of two combinations, combination one (atropine, Pralidoxime, magnesium sulphate) & combination-2(atropine and Pralidoxime) in organ phosphorous patients, the both combination shows equal effectiveness.

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