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A STUDY ON CLINICAL PROFILE AND OUTCOME OF INTERMEDIATE SYNDROME IN PATIENTS WITH ACUTE ORGANOPHOSPHATE POISONING

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ABSTRACT

Background and objective: Deliberate self-harm by ingestion of acute organophosphate poisoning is one of the common cause of death. The incidence of Intermediate syndrome (IMS) is high and is a major contributing factor for organophosphate-related morbidity and mortality. The data regarding the pathophysiology, clinical profile and outcome of patients with features of IMS remains elusive. Method: 40 patients showing features of Intermediate syndrome are subjected to detailed history and a systematic clinical examination after obtaining the informed consent. *Our study is to study the clinical profile and outcome of Intermediate syndrome and to correlate with various parameters.* Results: In our study maximum number of cases was in the age group 40-49, males (90%), from agriculture sector (70.0%), and the most common compound was Monocrotophos 40.0.Onset of intermediate syndrome ranges between 2-4 days, duration of IMS 3-20days. The common clinical presentation was proximal muscle weakness (100%) followed by neck muscle weakness (90%). 65.0% had developed ventilator acquired pneumonia (VAP) and Pseudomonas was most common organism. Interpretation and conclusion: Our study emphasis the importance of early recognition of IMS and initiation of treatment P_2AM and atropinisation decreases the duration of IMS and mortality. There was no correlation between the mode of poisoning, onset & duration of IMS, type of compound, respiratory failure, PChE level, ventilatory support duration and VAP and the occurance of intermediate poisoning or its outcome in our study. But it was inferred that increased amount of organophosphate consumed significantly affects occurrence of IMS and outcome.

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Keywords: Organophosphate poisoning, Intermediate syndrome

1.INTRODUCTION

According to the World Health Organisation (WHO), about 2 million people attempt to commit suicide and about one million poisoning occur every year worldwide. In Asia the most common and widely used poisoning is Organophosphates resulting in greater mortality rate (Ali, 2012).The American Association of Poison Control Centre has reported the highest incidence being in India(Faiz, 2011). Poisoning by Deliberate self-harm is the fourth most common cause of mortality among the rural population of India (Weiss and Parker, 1995; Siwach and Gupta, 1995).

Organophosphate compounds are widely used in agriculture for protection of crops and control of pests(Mogda et al., 2009). Some O P have been used in the treatment of myasthenia gravis, e.g. diisopropylphosphoro-fluoridate (DFP) (Comroe et al., 1946), tetraethyl pyrophosphate (TEPP) (Groband Harvey, 1949), and octomethylpyrophosphotetramide (OMPA) (Rider et al., 1951). The highly potent compounds, like tabun, sarin, soman have been used as "nerve gases", also been used as stabilizers in lubricating and hydraulic oils, plasticizers, flame retardants, and gasoline additives (De Bleeker et al., 1992). Increased use of pesticides have increased the yield in agriculture sector but at the cost of many lives. There are no strict rules and regulations for the purchase of these pesticides, inspite of them being a major cause of morbidity and mortality (Wadia,2003).

The organophosphates acts by inhibiting the acetylcholinesterase (AChE) activity, resulting in the accumulation of acetylcholine at the cholinergic synapses (Aminoff, 2004; Aygun et al., 2002). Manifestions of poisoning are characterized by a triphasic response, namely,

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acute cholinergic crisis, intermediate syndrome (IMS), and delayed polyneuropathy known as organophosphate-induced delayed neurotoxicity (OPIDN). Acute cholinergic crisis occurs within minutes to several hours after exposure, mainly affects the peripheral muscarinic and nicotinic receptors, and also the central nervous system, by inhibiting acetylcholinesterase. Manifestations of cholinergic crisis may include, vomiting, diarrhea, urinary incontinence, miosis, salivation, lacrimation, bronchorrhea, bradycardia, hypotension, fasciculation, muscle paralysis, confusion, seizures, and respiratory failure. Organophosphaterelated delayed polyneuropathy, known as organophosphate-induced delayed neurotoxicity (OPIDN), occurs after 2–3 weeks of exposure due to the inhibition of neuropathy target esterase. The clinical features of OPIDN are predominantly motor neuropathy and progressive ascending weakness of the limb muscles (Senanayake and Karalliedde, 1987).

In addition to the acute cholinergic crisis and OPIDN, organophosphate insecticides results in Intermediate syndrome IMS a term introduced by Senanayake and Karalliedde, (1987). IMS occurs as a result of impairment of neuromuscular transmission due to prolonged inhibition of AChE activity at the muscle end-plate. It is characterized by nicotinic effects such as weakness of the muscles of respiratory, bulbar, extraocular, neck and proximal limb and motor cranial nerves involvement (Aminoff, 2004; Aygun et al., 2002). Senanayake and Karalliedde have reported that the incidence of IMS could be as high as 80%(Senanayake and Karalliedde, 1987). Although the incidence of IMS may be high and a major contributing factor for organophosphate-related morbidity and mortality, the pathophysiology and data regarding clinical profile and outcome of patients that underlies IMS remains unclear.

AIMS AND OBJECTIVES:

1. To study the clinical profile of Intermediate syndrome in patients with acute organophosphate poisoning.
2. To assess the frequency of Occurrence of Intermediate syndrome in relation to various types of Organophosphate compounds.
3. To study the outcome of Intermediate syndrome in terms of recovery or death.
4. To correlate outcome of IMS with the Type of Compound, Quantity of the compound consumed, Duration of IMS, Respiratory failure, Serum Cholinesterase levels.

Study design: Observational study, **Sample size:** 40 patients showing features of Intermediate syndrome. **Study duration:** October 2015 – September 2017, **Study place:** Rajah Muthiah Medical College & Hospital.

Inclusion Criteria

1. Patients with Acute Organophosphate poisoning showing features of Intermediate syndrome in the form of Proximal muscle weakness, Respiratory failure, Extra ocular movement restriction, Neck flexors weakness.
2. Time since consumption of OPC more than 24 hrs and less than7 days

Exclusion Criteria

1. Patients in Cholinergic Crisis
2. Time since consumption of OPC more than 7 days
3. Patients who have consumed mixture of pesticide compounds /Organocarbamate compounds
4. Hypokalemia
5. Known cases of muscular dystrophy / myasthenia gravis
6. Patients with medical illness such as COPD, CVA.

2.METHODOLOGY

40 Patients who are eligible for the study are selected and are subjected to detailed history and a systematic clinical examination after obtaining the informed consent. Age, gender, type and quantity of compound consumed, onset &duration of IMS, serum cholinesterase levels, ventilator support, clinical features, and finally the outcome in terms of recovery, death of the patient are recorded. Routine investigations of the patients like complete blood count, renal function tests serum electrolytes and Serum cholinesterase are done. All the patients included in the study will be treated with as per the approved standard protocol with pralidoxime, atropine as required and with other supportive measures. Outcomes of the patients will be correlated with, factors mentioned above. **Statistical analysis:** A complete Statistical analysis was performed Percentage was used to express the qualitative variables. The quantitative variables were expressed as mean, standard deviation, and frequency of occurrence. Chi-square (x2) test was applied to test association between two categorical variables. Independent t-test was used to compare numerical variables between the two groups.

3.RESULTS

The age distribution in IMS patients was found to be that 2(5%) were below 19 years, 9(22.5%) in 20-29 years, 5(12.5%) in 30-39 years, 11(27.5%) in40-49 years, 10(25.0%) in 50 years and 3(7.5%) were 60 and above. There was a preponderance to poisoning in the males (90%) than in the females (10%). Occupational distribution of patients shows that 28 (70.0%) were from agriculture sector, 12(30.0%) were others. The exposure route was by oral ingestion and being intentionally in all 40 patients, out of which 35 recovered and 5 deaths occurred. But there was no correlation between the mode of poisoning and the occurance of intermediate poisoning or its outcome. In our study the most common type of the compound consumed was Monocrotophos 40.0%.others followed by chlorpyriphos 22.5%, Profenofos 12.5%, Dimethoate 10.0%, Phorate 7.5%, and Diethyl parathion, Quinolphos, and Malathion each 2.5%.

Quantum of exposure and outcome: In the observations from our study it is inferred that occurrence of Intermediate syndrome may occur with consumption of OP compounds of varying amounts from 40-160 ml (Table:1).

Table 1: Quantum of exposure and outcome

Quantity (ml)	Frequency (n)	Recovery	Death	Total
40-80ml	3	3(7.5%)	0	3(7.5%)
81-120ml	24	22(55%)	2(5%)	24 (60%)
121-160ml	8	7(17.5%)	1(2.5%)	8(20%)
>160ml	5	3(7.5%)	2(5%)	5(12.5%)
Total	40	35	5	40(100%)

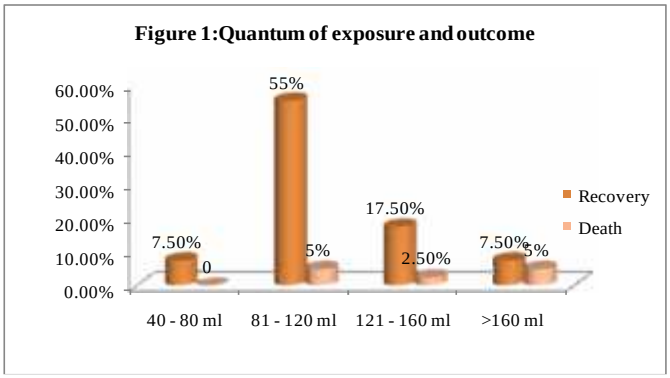

Fig. 1 Quantum of exposure and Outcome

The mean quantity of Organophosphate poisoning was 119.43±33.8 ml among those who recovered and 150±46.9 among those who died. An independent t test was used to find out the difference amount of consuming poison between survival and dead. The Levene's test shows that the variances between the two groups was equal the t-test reveals that the differences in mean quantity of consumption of organophosphate between survival and death was significant ($p<0.1$). Hence, it ican be inferred that consuming a higher quantity of organophosphate poisoning significantly leads to death. (Table 2, Figure 1)

Table 2: comparison of mean quantity of organophosphate poisoning by outcome

(t – test) Equality of variance	Levene's Test for Equality of Variances		t-test for Equality of Means					
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower / Upper
Equal variances assumed	2.143	.151	-1.807	38	.079	-30.571	16.919	-64.822 / 3.679
Equal variances not assumed			-1.406	4.612	.223	-30.571	21.739	-87.900 / 26.757

ONSET DAY and Duration of IMS Vs OUTCOME

Table 3: Duration of IMS and Outcome

S.No	Duration of IMS	Frequency	Recovery	Death
1	3-8 days	23(57.5%)	19(47.5%)	4(10%)
2	9-12 days	8(20%)	8(20%)	0
3	>12 days	9(22.5%)	8(20%)	1(2.5%)
Total		40(100%)	35(87.5%)	5(12.5%)

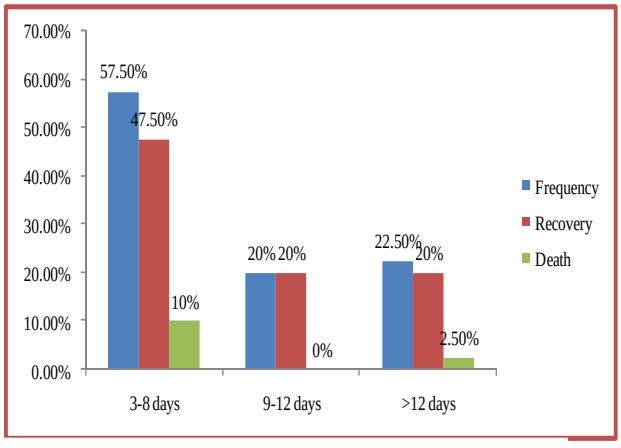

Fig.2: Duration of IMS and Outcome

Onset of intermediate syndrome ranges between 2-4 days of exposure. Independent t-test reveals that IMS onset day and outcome was not significant ($p>0.05$). An independent t test was used to find out the difference of duration of IMS between survival and died patients and was not significant ($p>0.05$). Leven's test shows that the variances of duration of IMS between the survived and died patients was not same. (Table: 3, Figure: 2).

Clinical features: In our study group, most common presentation was proximal muscle weakness (100%, n-40) followed by neck muscle weakness (90%, n-36), EOM restriction (65% n-26) and Bulbar palsy (50% n-20). Out of 33 patients who had respiratory failure 5 expired and 7 without respiratory failure all survived .Since Chi-square =0.0, df=1, p=1.0, there was no association between respiratory failure and survival status of the participants.

Table 4: PChE level by survival status

PChE level	Survival	Died	Total
Severe (0-1000 IU/L)	7(87.5%	1(12.5%)	8(100.0%)
Moderate(1001-2000 IU/L)	23(88.5%)	3(11.5%)	26(100.0%)
Mild (2000-3500 IU/L)	5(83.3%)	1(16.6%)	6(100.0%)
Total	35(87.5%)	5(12.5%)	40(100.0%)

Chi-square (LL) =0.117, df=2, p=0.943

The PChE level was categorized into severe, moderate and mild and normal. The association between PChE level and survival status was not significant ($p>0.05$). (Table: 4)

Ventilator support and Outcome of IMS 37 (92.5%) required mechanical ventilation and 3 (7.5%) did not require mechanical ventilation. The proportion of survival among those who received ventilation was 86.5% and that of not received was 100.0%. Chi-square test shows that the differences were not significant ($p=0.496$).

Table 5: Ventilator support and Outcome of IMS

S. No	Days on Ventilation	Total No. on Ventilator	Recovered	Expired	VAP frequency	Non VAP
1	<3 days	2	1	1	0	2
2	4-6 days	13	11	2	7	6
3	7-9 days	7	7	0	4	3
4	>9 days	15	13	2	15	0
	Total	37	32	5	26	11

t-test reveals that the differences in mean number of days on ventilation between survival and died was not significant ($p>0.05$) .Among the ventilated patients, 65.0% developed ventilator acquired pneumonia (VAP). Pseudomonas was found in 19 patients, klebsiella in 5 patients, MRSA and E.coli in one patient each. Chi-square test reveals that there was no association between ventilator developed pneumonia and survival status.

4.DISCUSSION

Our study was conducted in 40 patients with Intermediate

syndrome following acute Organophosphate poisoning. Patients were closely monitored and the parameters included in the methodology were assessed. The following observations were found in our study.

AGE AND GENDER DISTRIBUTION: Of the 40 patients, maximum frequency of cases was observed in the age group between 40-60 years. In the studies by Quinby (1968), Balani *et al*. (1968), Gupta and Patel (1965) reported that the peak incidence of poisoning was by the third decade of life. Goel *et al*. concluded that maximum incidence was in the second and third decade[14]. But in our study maximum incidence was in 40-49 years of age. This age group predilection may be due to more vulnerability to psychological stress, ability to cope up with the emotional conflicts and tough situations that ultimately force him/her to end his life by some mode .In our study out of the 40 patients , 90% (n-36)were found to be males, 10% (n-4) were females. The outcome of IMS is determined by neither the age nor the sex of the patients in the study (p value >0.05).A similar observation was reported by Senanayake et al in 1987[15],Mutalik*et al.* (1962), Gupta and Patel (1968), Balani *et al*. (1968),41 and Goel *et al.* (1998) that consumption of poisoning had been predominant in males in their study. In contrast to this Vishwanathan and Shrinivasan (1962) reported that higher incidence was among the female than males (Soni and Solu,2016).

OCCUPATION: From the observations of our study 28(70%) cases out of 40 patients had agriculture as their occupation and the rest 12(30%) out of 40 were from nonagriculture sector. The reasons for the increased consumption of poisoning and mortality among them may be due minimal access to the health care providers in the rural areas and also lack of awareness about the measures in managing the patients of acute poisoning.

ROUTE AND MODE OF EXPOSURE: There are many routes of exposure to poisoning like the oral ingestion, inhalational, dermal contact, intravenous and aural ingestion but in this study on patients of IMS all the 40(100%) patients had oral ingestion and had consumed intentionally by deliberate self-harm. Goel *et al*. reported that organophosphorus compound was consumed intentionally by 96% and the rest 4% was due to occupational exposure[16].But there was no correlation between the mode of poisoning and the occurance of intermediate poisoning or its outcome. This is in concordance with the WHO estimate which states that out of the three million cases/ year due to the pesticide poisoning , nearly about two third of the total cases had an intentional mode of consumption ofpoisoning (Michael Eddleston et al., 1998).

QUANTUM OF EXPOSURE: From our study it is inferred that occurrence of Intermediate syndrome may occur with consumption of OP compounds of varying amounts from 40-160ml. The t-test reveals that the differences in mean quantity of consumption of organophosphate between survival and death was significant (p<0.1). Hence, it can be inferred that consuming a higher quantity of organophosphate poisoning significantly leads to death. Therefore patients admitted with increased amount of consumption of OPCs needs strict monitoring and aggressive management from the time of admission until recovery.

TYPE OF COMPOUND: Monocrotophos was the most common OP compound in our study resulting in IMS constituting to about 40%. This is in contrast to a retrospective study conducted in Mangalore, Karnataka on IMS patients in which the most common compound resulting in IMS was metyl parathion (Wadia et al., 1974).

ONSET AND DURATION OF INTERMEDIATE SYNDROME: From the observations it is inferred that IMS occurs between day 2-4 of exposure and duration of IMS in our study was between 3 – 18 days. Independent t-test reveals the differences in mean duration of IMS Of acute Organophosphate poisoning between recovery and death was not significant (p>0.05).

Frequency of Occurrence of individual Clinical Parameter: In our study, the most common clinical presentation was proximal muscle weakness (100%, n-40) which was similar to the studies of Wadia et al (1974; Shailesh et al., 1994).Other manifestations were neck muscle weakness (90%, n-36), extraocular muscle restriction was (65%,n-26) and bulbar palsy was seen in (50%,n-20).Respiratory failure was the most common complication in patients of OP poisoning that develops in 24 hours of exposure. Cholinergic over activity results in the early onset of respiratory failure whereas the late onset respiratory failure may be attributed to the respiratory infections. Shaileesh et al, (2009; Wadia et al (1974) have concluded that mortality in Intermediate syndrome in majority of the cases in their study was due to respiratory failure. In our study there was no association between respiratory failure and survival status of the participants.

Frequency of patients needed mechanical ventilation and outcome: Among the 40 study population in our study 37 required mechanical ventilation. However, the Chi-square test shows that the differences were not significant (p=0.496). Regarding duration of ventilator support it varied from 2-30 days .Independent t-test reveals that the differences in mean number of days on ventilation between those recovered and those dead was not significant (p>0.05).

VAP AND OUTCOME ANALYSIS: Patients on prolonged mechanical ventilator support are prone to develop associated complications like the VAP (Ventilator Associated Pneumonia). Out of the 37 patients who required mechanical ventilation, 26 patients developed VAP. Pseudomonas was the most common organism found others were klebsiella, MRSA and E.coli . Correlation between VAP and Outcome was not statistically significant (p=0.591).

PChE AND OUTCOME: PChE levels were analysed for association with outcome in patients of IMS and found that the association between PChE level and survival status was not significant (p>0.05).This was similar to the results of a prospective study which was conducted in Chennai, Tamilnadu where it was inferred that the serum cholinesterase levels had no significant association with the occurrence of Intermediate syndrome (Aygun et al., 2002).

5.CONCLUSION

1. Out of the 40 IMS patients of acute OP poisoning majority were in the age of 40-49 years and mostly males (90%).
2. Monocrotophos was the frequent compound encountered with IMS. Type of compound, route and mode of exposure had no association with outcome of IMS.
3. Quantum of exposure >80ml affects significantly the outcome of patients in Intermediate syndrome. There was a statistical significance ($p<0.1$) between difference in mean quantity of consumption of organophosphate between survival and death. The higher the quantity of organophosphate consumed significantly leads to death.
4. Day of onset was 24 -96 hours since exposure, duration of IMS was between 3-18 days. It may be concluded that the IMS onset day and mean duration of IMS did not have any influence the outcome as it was not significant ($p>0.05$).
5. Proximal muscle weakness followed by neck muscle weakness was the most common presentation observed in our study.
6. Outcome of IMS was independent of Serum cholinesterase levels
7. Though respiratory failure in IMS is a risk factor for mortality in Intermediate syndrome and significantly affects the outcome in many other studies, in our study there was no association between respiratory failure and survival status which may be due to early and proper ventilatory support and care.
8. Duration of ventilator support and development of ventilator associated pneumonia had no impact on the outcome of IMS. Among those, who developed VAP the most common organism found was Pseudomonas.

Our study emphasis the importance of providing health education to the people in the rural areas to decrease the incidence of cases among the people of agricultural sector. Also early recognition of IMS and initiation of appropriate treatment with high dose P2AM, proper atropinisation and ventilator support results in decrease in the duration of the patient in IMS and mortality.

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