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A Study On The Clinical Profile And Outcome Of Intermediate Syndrome In Patients With Acute Organophosphate Poisoning.

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ABSTRACT

Deliberate self-harm by ingestion of acute organophosphate poisoning is one of the common causes 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. **:**40 patients showing features of Intermediate syndrome are subjected to detailed history and a systematic clinical examination after obtaining informed consent. Our study is to study the clinical profile and outcome of Intermediate syndrome and to correlate with various parameters. In our study, the maximum number of cases was in the age group 40-49, males (90%), from the agriculture sector (70.0%), and the most common compound was Monocrotophos 40.0. The onset of intermediate syndrome ranges between 2-4 days, duration of IMS is 3- 20 days. 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 the most common organism. Our study emphasises the importance of early recognition of IMS and initiation of treatment P2AM and atropinization 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 occurrence of intermediate poisoning or its outcome in our study. But it was inferred that an increased amount of organophosphate consumed significantly affects the occurrence of IMS and its outcome.

Keywords: Organophosphate poisoning, Intermediate syndrome.

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INTRODUCTION

According to the World Health Organisation (WHO), about 2 million people attempt to commit suicide and about one million poisonings occur every year worldwide. In Asia, the most common and widely used poisoning is Organophosphates resulting in a greater mortality rate [1]. The American Association of Poison Control Centre has reported the highest incidence being in India [2]. Poisoning by Deliberate self-harm is the fourth most common cause of mortality among the rural population of India [3,4]. Organophosphate compounds are widely used in agriculture for the protection of crops and the control of pests [5]. Some OP has been used in the treatment of myasthenia gravis, e.g. diisopropyl phosphoro-fluoridate (DFP), tetraethyl pyrophosphate (TEPP), and octomethyl pyrophosphotetramide (OMPA) [6-8]. The highly potent compounds, like tabun, sarin, and soman have been used as "nerve gases", and also been used as stabilizers in lubricating and hydraulic oils, plasticizers, flame retardants, and gasoline additives [9]. Increased use of pesticides has increased the yield in the agriculture sector but at the cost of many lives. There are no strict rules and regulations for the purchase of these pesticides, despite them being a major cause of morbidity and mortality [10]. The organophosphates act by inhibiting the acetylcholinesterase (AChE) activity, resulting in the accumulation of acetylcholine at the cholinergic synapses [11,12]. Manifestations of poisoning are characterized by a triphasic response, namely, 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 and 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. Organophosphate-related 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 [13].

METHODOLOGY

In this Observational study, 40 Patients showing features of Intermediate syndrome who are eligible for the study are selected and are subjected to detailed history and a systematic clinical examination after obtaining informed consent at the Department of General Medicine, Government Tiruvannamalai Medical College, Tiruvannamalai, Tamil Nadu India in the year 2022. Age, gender, type and quantity of compound consumed, onset & duration of IMS, serum cholinesterase levels, ventilatory support, clinical features, and finally the outcome in terms of recovery, and 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 as per the approved standard protocol with pralidoxime atropine as required and with other supportive measures. Outcomes of the patients will be correlated with, the 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. The Chi-square (x2) test was applied to test the association between two categorical variables. Independent t-test was used to compare numerical variables between the two groups.

Inclusion Criteria

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

Exclusion Criteria

- Patients in Cholinergic Crisis
- Time since consumption of OPC more than 7 days

- Patients who have consumed a mixture of pesticide compounds /Organocarbamate compounds
- Hypokalemia
- Known cases of muscular dystrophy/myasthenia gravis
- Patients with medical illnesses such as COPD, and CVA.

OBSERVATION AND 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%) in 40-49 years, 10(25.0%) in 50 years and 3(7.5%) were 60 and above. There was a preponderance of poisoning in the males (90%) than in the females (10%). The occupational distribution of patients shows that 28 (70.0%) were from the agriculture sector, and 12(30.0%) were from others. The exposure route was by oral ingestion and intentionally in all 40 patients, out of which 35 recovered and 5 deaths occurred. However, there was no correlation between the mode of poisoning and the occurrence 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 the occurrence of Intermediate syndrome may occur with the consumption of OP compounds of varying amounts from 40-160 ml (Table).

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%)

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						
								95% Confidence Interval of the Difference	
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error 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

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 poison between survival and death. Levene's test shows that the variances between the two groups were equal the t-test reveals that the differences in the mean quantity of consumption of organophosphate between survival and death were significant ($p<0.1$). Hence, it can be inferred that consuming a higher quantity of organophosphate poisoning significantly leads to death. (Table 2)

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Table 3: Duration of IMS and Outcome

S.no	Duration of IMS	Frequency	Percentage	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%)

Table 3: 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 in duration of IMS between survival and dead patients and was not significant (p>0.05). Leven's test shows that the variances in the duration of IMS between the survived and dead patients were not the same. In our study group, the 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 the 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 mild, and normal. The association between PChE level and survival status was not significant (p>0.05). (Table: 4)

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

Table independent t-test reveals that the differences in the mean number of days on ventilation between survival and death were 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, and MRSA and E. coli in one patient each. The chi-square test reveals that there was no association between ventilator-developed pneumonia and survival status.

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. Of the 40 patients, the 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 the maximum incidence was in the second and third decades [14]. However, in our study, the maximum incidence was 40-49 years of age. This age group predilection may be due to more vulnerability to psychological stress and, the ability to cope with the emotional conflicts and tough situations that ultimately force him/her to end his life in some mode. In our

study out of the 40 patients, 90% (n-36) were found to be males, and 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 a higher incidence was among females than males [14]. There are many routes of exposure to poisoning oral ingestion, inhalational, dermal contact, intravenous, and aural ingestion but in this study on patients of IMS, all 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]. However, there was no correlation between the mode of poisoning and the occurrence 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 pesticide poisoning, nearly about two third of the total cases had an intentional mode of consumption of poisoning [17]. 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 the mean quantity of consumption of organophosphate between survival and death were 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 amounts of consumption of OPCs need strict monitoring and aggressive management from the time of admission until recovery. Monocrotophos was the most common OP compound in our study resulting in IMS constituting 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 methyl parathion [18]. From the observations it is inferred that IMS occurs between days 2-4 of exposure and duration of IMS in our study was between 3 – 18 days. Independent t-test reveals the differences in the mean duration of IMS Of acute Organophosphate poisoning between recovery and death were not significant ($p>0.05$). 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 and Shailesh Kk et al [18,19]. Other manifestations were neck muscle weakness (90%, n-36), extraocular muscle restriction (65%,n-26), and bulbar palsy was seen in (50%,n-20). Respiratory failure was the most common complication in patients with OP poisoning develops within 24 hours of exposure. Cholinergic overactivity results in the early onset of respiratory failure whereas the late onset of respiratory failure may be attributed to respiratory infections. Shailesh et al, and Wadia et al concluded that mortality in Intermediate syndrome in the majority of the cases in their study was due to respiratory failure. In our study, there was no association between respiratory failure and the survival status of the participants. 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 the 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 ($p>0.05$). Patients on prolonged mechanical ventilator support are prone to develop associated complications like 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. The correlation between VAP and Outcome was not statistically significant ($p=0.591$). PChE levels were analyzed for association with outcomes 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, Tamil Nadu where it was inferred that the serum cholinesterase levels had no significant association with the occurrence of Intermediate syndrome [20].

CONCLUSION

Quantum of exposure >80ml affects significantly the outcome of patients with Intermediate syndrome. There was a statistical significance ($p<0.1$) between the difference in the mean quantity of consumption of organophosphate between survival and death. The higher the quantity of organophosphate consumed significantly leads to death. 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 on the outcome as it was not significant ($p>0.05$). 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. 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 emphasizes the importance of providing health education to people in rural areas to decrease the incidence of cases among people in the agricultural sector. Also, early recognition of IMS and initiation of appropriate treatment with high dose P2AM, proper atropinisation, and ventilator support results in a decrease in the duration of the patient in IMS and mortality.

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