ORIGINAL ARTICLE

# Clinical profile of Intermediate Syndrome following Organophosphate Poisoning

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## Abstract

*Background:* Organophosphate (OP) poisoning is a global issue, causing over 200,000 deaths annually especially in developing countries, such as Sri Lanka and India. Clinical presentation of a typical OP poisoning may follow three well-defined phases. The initial phase is an acute cholinergic crisis, after that Intermediate Syndrome (IMS) may develop within 24-96 hours, and lastly, Organophosphate-Induced Delayed Polyneuropathy (OPIDPN) may present after 2-3 weeks. The signs and symptoms of the IMS are weakness of the respiratory muscles, including the diaphragm, intercostal, accessory, neck, and proximal limbs muscles. The aim of this study was to highlight the clinical profile of the IMS following organophosphate poisoning.
*Methods:* This descriptive, prospective, and cross-sectional study was conducted at the Teaching Hospital, Batticaloa, Sri Lanka, over a period of 6 months from March 1, 2017 to August 31, 2017.
*Results:* Of the total 65 enrolled patients, 60% (n=39) were male. All patients ingested OP pesticide for deliberate self-harm and all of them had some degrees of initial cholinergic crises. The prevalence of IMS in the studied patients was 5.88%. All 5 patients with IMS had neck, facial and proximal limbs muscle weakness from whom, two cases (40%) had extra-ocular muscle paralysis. There was no in-hospital fatality among IMS patients.
*Conclusion:* IMS is a rare and life-threatening problem in OP intoxication. Early diagnosis and intensive care management can prevent further complications and mortality. Prevalence of IMS in this study was lower than previous reports with almost similar clinical features.

**Keywords:** Intermediate Syndrome; Organophosphate Poisoning

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## INTRODUCTION

Organophosphate (OP) poisoning is a global issue, causing over 200,000 deaths annually (1). In the developing world, these events are more prevalent and connected with higher mortality rates.

Acetylcholine (ACh) is a neurotransmitter present at the neuromuscular junctions in peripheral and central nervous systems. Acetylcholinesterase (AChE) is an enzyme that usually hydrolyzes and breaks down ACh. Organophosphorus compounds cause phosphorylation and inactivation of AChE leading to the accumulation of ACh which is responsible for the clinical presentations of the cholinergic syndrome (2). Typical OP poisoning is followed by three well-defined clinical phases. The first phase manifests as a cholinergic syndrome; the symptoms include miosis, nausea, vomiting, diarrhea, dyspnea, and bradycardia. Seizure, coma, and respiratory failure may also occur (3). Secondly, the Intermediate Syndrome (IMS), comprised of characteristic signs and symptoms occurs following evident recuperation from intense cholinergic disorder. As the disorder occurs following the initial phase and before the last phase, it is called 'Intermediate Syndrome'. Thirdly, OP-Induced Delayed Poly-Neuropathy (OPIDPN) develops at several weeks after exposure (4). OPIDPN is an occasional neurotoxicity effect, happening 1 to 6 weeks following acute cholinergic crisis resulting in muscle weakness, pain, and paresthesia. The reason behind this postponed impact is the phosphorylation of sensory tissue proteins bringing about Wallerian axonal degeneration (5, 6). However, OPIDPN is reported to persist after two years of follow-up (7).

The IMS happens in roughly 20% of patients after an oral closeness to OP pesticides; however, there is no unmistakable relationship between the specific OP pesticide exposure and the advancement of the disorder (8). It typically sets up 2-4 days after closeness when the manifestations of the intense cholinergic disorder are not anymore self-evident (9). Of the signs and symptoms of the IMS is weakness of the respiratory muscles such as the diaphragm, intercostal, accessory, neck, and proximal limb muscles. The underlying pathology behind the Intermediate Syndrome (formerly named Nicotinic Syndrome) is that it requires hindrance of minimum 80% of the synaptic AChE. Therefore, it is understandable that the nicotinic disorder happens just in acute poisonings. The outcome is hyperstimulation of the neuromuscular junctions by inordinate ACh, principally bringing about fasciculations,

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which is later trailed by neuromuscular loss of motion; the influence of IMS may be present for 2-18 days (10). The aim of this study was to highlight the clinical profile of the IMS following organophosphate poisoning.

## METHODS

This descriptive, prospective, and cross-sectional study was conducted at Batticaloa, Teaching Hospital, Sri Lanka, over the period of 6 months from March 1, 2017 to August 31, 2017. Patients, with less than 12 years of age and pregnant patients were excluded from this study. Informed written consents were obtained from all included patients. Though it was initially not possible to get consent from the patients, it was obtained from the accompanying relatives. However, later we attempted to get consent from the patients once they regained their consciousness. The consent was taken from the head of the institution for conducting this study as well.

OP poisoning was affirmed by the medical background from the patient as well as relatives, containers brought to the healing facility, records in patient-exchange forms, the specific smell in the breath, and clinical signs and symptoms normally found in OP poisoning. Based on Senanayake and Karalliedde's original remarks, a possible diagnosis for IMS was made, namely specific muscle weakness in minimum three of the muscle groups below (extraocular, neck flexor, proximal limb, and facial) witnessed minimum 24 h following the intake of OP pesticide (11). As per the Medical Research Council [MRC] grading, the weakness of proximal muscles and neck flexion was viewed as notable when the muscle power was grade 3 or less (3).

Patients' demographic data were collected using a self-administered validated questionnaire. We included all adults and adolescents, aged 12 years or more with deliberate self-harm (DSH) with definite organophosphate poisoning. Any patient with uncertainty regarding the type of poisoning was excluded from the study. The clinical signs and symptoms of IMS were collected from the medical records. The amount of ingested pesticide was asked from the patient; however, this was not an accurate method. That said, it might have a relation to the occurrence of the IMS. The data were analyzed by the descriptive statistical method using SPSS 19 software. The results were presented as frequency and percentage.

## RESULTS

Of the total 65 patients recruited, 60% (n = 39) were male and 40% (n = 26) were female. All patients were poisoned through the gastrointestinal route. The prevalence of IMS among OP poisoning was 5.88% (n = 5). It was obvious that IMS was more prevalent in males (80%) (n = 4) than females (20%) (n = 1). The estimated average time for admission to the emergency department after the exposure to OP pesticide was 7.6 hours. In our study, almost all IMS patients required ventilatory support. The most frequent initial clinical signs were meiosis (100%), change in mental status (100%), hypersalivation (100%), agitation (60%) and fasciculations (60%) (Table 1). Out of five IMS patients, only one patient developed acute kidney injury. There was no in-hospital fatality among IMS patients in our study.

**Table 1. Clinical profile of patients with intermediate syndrome following organophosphorus compounds intoxication**

| Clinical Profile | Case-1 | Case-2 | Case-3 | Case-4 | Case-5 |
|---|---|---|---|---|---|
| Sex | male | male | female | male | male |
| Age (years) | 53 | 27 | 23 | 45 | 20 |
| Acute renal failure | - | + | - | - | - |
| Neck muscle weakness | + | + | + | + | + |
| Extraocular muscle weakness | - | - | + | - | + |
| Proximal muscle weakness | + | + | + | + | + |
| Facial muscle weakness | + | + | + | + | + |
| Average time interval between time of poisoning and hospital admission (hours) | 8 | 12 | 5 | 7 | 6 |
| Myocarditis | - | - | - | - | - |
| ARDS | - | - | + | + | - |
| Epileptic movements | + | - | - | - | - |
| Meiosis | + | + | + | + | + |
| Ventilatory support | + | + | + | + | + |
| Change in mental status | + | + | + | + | + |
| Hypersalivation | + | + | + | + | + |
| Agitation | + | + | + | - | - |
| Fasciculations | + | - | + | - | + |
| Duration of mechanical ventilation (days) | 4 | 7 | 5 | 8 | 4 |
| Acute renal failure | - | + | - | - | - |

## DISCUSSION

In the neuromuscular junction (NMJ), acetylcholine is discharged when a nerve impulse gets to the terminal axonal end and it scatters over the synaptic split and ties to cholinergic nicotinic receptors on the muscle filaments (10). In the subsequent classical OP poisoning, three clearly characterized clinical stages are observed, initial intense cholinergic crisis, the IMS and OPIDPN. In 1987, IMS was described in Sri Lanka by Senanayake and Karalliedde.(11) According to the study conducted by Umakanth M, the prevalence of OP poisoning among DSH in the east part of Sri Lanka was 19% (12, 13).

Intermediate Syndrome develops 24-96 hours after exposure and imitates a prolonged action of ACh on the nicotine receptors. The clinical features are muscular weakness in the ocular, neck, bulbar, proximal limb and respiratory muscles (9). It is presently apparent that the degree and extent of muscle weakness may change after the IMS has begun (9). In our study, the prevalence of IMS among OP poisoning was 5.88%. This percentage is less than that of the study conducted by Pradeepa Jayawardane, where prevalence was reported at 8.8% (8). However, the reported frequency of IMS varies from 8% to 49% (14-16).

Some patients may just experience weakness of neck muscles, while others may have weakness of neck muscles and proximal limb muscles (14). However, in this study, all patients had weakness of proximal limbs muscles, neck muscles, and facial muscles. Most patients with IMS develop respiratory failure, which requires mechanical ventilation. In this study, mechanical ventilatory support was needed for all 5 IMS patients. The average duration of mechanical ventilation was 5.6 days. Most of the deaths from acute OP poisoning could be attributed substantially to respiratory failure through the following effects: depression of the respiratory center in the brainstem, neuromuscular paralysis, excessive respiratory secretions, and bronchoconstriction (17). Our patient presented respiratory failure on the 4th to 7th day of poisoning which is the average length for Intermediate Syndrome. However, out of five IMS patients, no patient died in this study.

OP can influence other organ systems which, although rare, can worsen the presentation and prognosis of the patient. One of the organs affected are the kidneys. Although the exact mechanism of acute kidney injury (AKI) is unclear, numerous hypotheses have been proposed. In our study, only one IMS patient developed acute kidney injury. One cohort study found that patients with OP poisoning had a 6.17 fold higher risk of AKI compared with the comparison cohort (17).

However, our study had some limitations. The types and amount of ingested OP pesticides were not known in most instances. The lower prevalence of observed IMS in our studied patients might be related to the smaller amount or lower toxicity of the ingested pesticides. Further investigation will be required to elucidate these limitations.

## CONCLUSION

Intermediate Syndrome (IMS) after organophosphorus pesticides intoxication develops 24-96 hours after resolution of cholinergic crises. In IMS, typically muscles of the neck, proximal limbs, and eyes, bulbar and respiratory groups are influenced. Patients with acute organophosphate poisoning may present deferred cholinergic signs and symptoms which would require a great deal of atropine administered. A careful assessment of clinical characteristics would be expected to titrate the dose down and stop it. Furthermore, intensive follow-ups would be required for uncommon side effects of organophosphate poisoning including IMS and organophosphate-induced delayed polyneuropathy.

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