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Original Research Article

Determinants of Intermediate Syndrome in Patients with Organophosphorus Poisoning: A Hospital-Based Study

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Abstract

Background: Organophosphorus (OP) poisoning remains a significant public health concern, particularly in agricultural communities. Intermediate syndrome (IMS) is a potentially fatal complication occurring 24-96 hours after acute OP exposure, characterized by proximal muscle weakness and respiratory failure. Identifying determinants of IMS development is crucial for early intervention and improved patient outcomes.

Methods: This prospective observational study was conducted at the toxicology unit of a tertiary care hospital over an 18-month period. A total of 142 patients with confirmed OP poisoning were enrolled. Demographic characteristics, clinical parameters, type of OP compound, time to treatment initiation, cholinesterase levels, and treatment modalities were analyzed. Patients were monitored for IMS development using standardized clinical criteria. Statistical analysis included chi-square tests, independent t-tests, and multivariate logistic regression.

Results: The incidence of IMS was 23.9% (n=34). Patients who developed IMS had significantly lower serum cholinesterase levels at admission (412.6 ± 187.3 U/L vs. 1089.4 ± 342.8 U/L; $p<0.001$). Delayed presentation (>6 hours) was significantly associated with IMS development ($p=0.002$). Dimethyl compounds showed higher IMS incidence compared to diethyl compounds (31.2% vs. 14.7%; $p=0.018$). Multivariate analysis revealed that ingested quantity (OR=3.42; 95% CI: 1.87-6.24), inadequate atropinization (OR=4.18; 95% CI: 2.11-8.27), and low admission cholinesterase (OR=2.89; 95% CI: 1.56-5.35) were independent predictors of IMS.

Conclusion: Multiple clinical and treatment-related factors determine IMS development in OP poisoning. Early presentation, adequate atropinization, and close monitoring of patients with severely depressed cholinesterase levels may reduce IMS incidence and improve survival outcomes.

Keywords: Organophosphorus poisoning, Intermediate syndrome, Cholinesterase, Atropine, Risk factors, Toxicology.

Introduction

Organophosphorus (OP) compound poisoning constitutes a major global health burden, accounting for approximately 200,000 deaths annually worldwide [1]. These compounds, widely utilized as agricultural pesticides, exert their toxic effects through irreversible inhibition of acetylcholinesterase enzyme, leading to accumulation of acetylcholine at synaptic junctions [2]. The clinical manifestations of OP poisoning encompass acute cholinergic crisis, intermediate syndrome (IMS), and delayed peripheral neuropathy [3].

Intermediate syndrome was first described by Senanayake and Karalliedde in 1987 as a distinct clinical entity occurring 24 to 96 hours following acute OP exposure [4]. The syndrome is characterized by weakness of proximal limb muscles, neck flexors, respiratory muscles, and cranial nerve-innervated muscles, occurring after resolution of the initial cholinergic crisis but before the onset of delayed neuropathy [5]. The reported incidence of IMS varies considerably, ranging from 10% to 68% across different studies, depending on the population studied and diagnostic criteria employed [6].

The pathophysiology of IMS remains incompletely understood. Proposed mechanisms include persistent acetylcholinesterase inhibition, pre-synaptic and post-synaptic dysfunction at the neuromuscular junction, muscle necrosis, and

oxidative stress-induced damage [7]. Recent electrophysiological studies have demonstrated decremental responses on repetitive nerve stimulation, suggesting a predominantly pre-synaptic defect [8].

Several factors have been implicated in IMS development, including the type of OP compound, quantity ingested, delay in treatment initiation, and adequacy of antidotal therapy [9]. However, the relative contribution of these factors and their interactions remain poorly characterized. Previous studies have yielded conflicting results regarding predictors of IMS, partly due to heterogeneous study populations and varying definitions of the syndrome [10].

The significance of identifying IMS determinants lies in the potential for early intervention and prevention. Patients developing IMS require prolonged mechanical ventilation and intensive care, significantly increasing morbidity, mortality, and healthcare costs [11]. Early identification of high-risk patients could facilitate closer monitoring and potentially preventive strategies.

Despite considerable research in this field, significant knowledge gaps persist regarding modifiable risk factors and their relative importance in determining IMS development. Furthermore, data from resource-limited settings, where OP poisoning is most prevalent, remain scarce [12]. The present study aimed to identify clinical, biochemical, and treatment-related determinants of intermediate syndrome in patients presenting with acute OP poisoning to a tertiary care hospital.

Materials and Methods

Study Design and Setting: This prospective observational study was conducted at the Medical Intensive Care Unit of a tertiary care teaching hospital.

Sample Size Calculation: Based on previous literature reporting IMS incidence of approximately 20-25%, with 95% confidence interval and 8% margin of error, the minimum required sample size was calculated as 120 patients. Accounting for potential dropouts and incomplete data, a target enrollment of 150 patients was planned.

Inclusion Criteria: Patients aged 18 years or above presenting with acute OP compound poisoning, confirmed by history of exposure and characteristic clinical features of cholinergic toxidrome, were included. Both intentional and accidental exposures were considered eligible.

Exclusion Criteria: Patients with mixed poisoning (multiple compounds), those with pre-existing neuromuscular disorders, chronic OP exposure, pregnancy, and those who died within 24 hours of admission before IMS assessment could be completed were excluded. Patients discharged against medical advice before completion of the observation period were also excluded.

Data Collection: A structured proforma was utilized to collect demographic data (age, sex, occupation), poisoning characteristics (compound type, route, estimated quantity, intent), clinical parameters (time of exposure, time to hospital presentation, vital signs, severity grading using Peradeniya Organophosphorus Poisoning Scale), biochemical parameters (serum cholinesterase levels at admission and serially thereafter, arterial blood gases), and treatment details (atropine dosage, pralidoxime administration, mechanical ventilation requirement).

Definitions: Intermediate syndrome was diagnosed based on clinical criteria: development of weakness of proximal limb muscles, neck flexors, and/or respiratory muscles occurring 24-96 hours after OP exposure, following initial stabilization from the acute cholinergic phase. Adequate atropinization was defined as achieving and maintaining target endpoints (clear lung fields, heart rate >80/min, systolic blood pressure >80 mmHg, dry axillae) within the first 6 hours of presentation.

Monitoring Protocol: All patients were monitored for a minimum of 7 days or until discharge. Clinical assessment for IMS was performed every 8 hours during the high-risk period (24-120 hours post-exposure). Respiratory function was assessed using bedside spirometry where feasible, and single-breath count test for cooperative patients.

Statistical Analysis: Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation and compared using independent samples t-test. Categorical variables were expressed as frequencies and percentages, compared using chi-square test or Fisher's exact test as appropriate. Variables significant on univariate analysis ($p<0.10$) were entered into multivariate binary logistic regression to identify independent predictors. A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics: During the study period, 168 patients with OP poisoning were screened, of whom 142 met inclusion criteria and were enrolled.

The mean age was 34.6 ± 12.8 years, with male predominance (62.0%, n=88). Intentional self-harm was the most common mode of poisoning (82.4%, n=117). Agricultural workers constituted 58.5% of the study population.

Incidence and Clinical Features of IMS: Intermediate syndrome developed in 34 patients

(23.9%). The mean time to IMS onset was 48.2 ± 18.6 hours post-exposure. Neck flexor weakness was the most common initial manifestation (91.2%), followed by proximal limb weakness (85.3%) and respiratory muscle weakness (67.6%). Twenty-three patients (67.6%) with IMS required mechanical ventilation, with a mean ventilation duration of 8.4 ± 4.2 days.

Comparison of Clinical Characteristics: Table 1 presents the comparison of demographic and clinical characteristics between patients with and without IMS. Patients developing IMS were significantly younger and more likely to have ingested larger quantities of OP compounds.

Table 1: Demographic and Clinical Characteristics of Patients With and Without Intermediate Syndrome

Variable	IMS Group (n=34)	Non-IMS Group (n=108)	p-value
Age (years), mean ± SD	31.2 ± 10.4	35.7 ± 13.4	0.042
Male sex, n (%)	24 (70.6)	64 (59.3)	0.236
Agricultural occupation, n (%)	23 (67.6)	60 (55.6)	0.208
Intentional ingestion, n (%)	31 (91.2)	86 (79.6)	0.124
Estimated quantity ingested (mL), mean ± SD	78.4 ± 42.6	41.2 ± 28.3	<0.001
Time to presentation (hours), mean ± SD	5.8 ± 3.2	3.4 ± 2.1	<0.001
Delayed presentation (>6 hours), n (%)	18 (52.9)	28 (25.9)	0.002
Peradeniya Score ≥8, n (%)	26 (76.5)	42 (38.9)	<0.001
GCS at admission, mean ± SD	11.2 ± 3.1	13.4 ± 2.2	<0.001

Biochemical Parameters: Serum cholinesterase levels at admission were significantly lower in patients who subsequently developed IMS. Table 2 demonstrates the comparison of biochemical parameters between the two groups.

Table 2: Biochemical Parameters in Patients With and Without Intermediate Syndrome

Parameter	IMS Group (n=34)	Non-IMS Group (n=108)	p-value
Admission serum cholinesterase (U/L), mean ± SD	412.6 ± 187.3	1089.4 ± 342.8	<0.001
Cholinesterase <500 U/L, n (%)	24 (70.6)	22 (20.4)	<0.001
Cholinesterase at 48 hours (U/L), mean ± SD	498.2 ± 224.6	1456.8 ± 412.4	<0.001
Arterial pH at admission, mean ± SD	7.28 ± 0.12	7.36 ± 0.08	<0.001
PaCO2 (mmHg), mean ± SD	48.6 ± 12.4	38.2 ± 8.6	<0.001
Serum lactate (mmol/L), mean ± SD	3.8 ± 1.6	2.1 ± 1.2	<0.001
Serum creatinine (mg/dL), mean ± SD	1.4 ± 0.8	1.1 ± 0.4	0.024

Type of Compound and Treatment Factors: Dimethyl OP compounds were associated with significantly higher IMS incidence compared to diethyl compounds. Inadequate atropinization was strongly associated with IMS development. Table 3 presents compound types and treatment-related factors.

Table 3: Type of Compound and Treatment Factors Associated with Intermediate Syndrome

Variable	IMS Group (n=34)	Non-IMS Group (n=108)	p-value
Type of OP Compound			
Dimethyl compounds, n (%)	24 (70.6)	53 (49.1)	0.018
Diethyl compounds, n (%)	8 (23.5)	46 (42.6)	0.018
Unknown/Mixed, n (%)	2 (5.9)	9 (8.3)	0.634
Specific Compounds			
Chlorpyrifos, n (%)	11 (32.4)	32 (29.6)	0.762
Monocrotophos, n (%)	9 (26.5)	14 (13.0)	0.056
Dimethoate, n (%)	6 (17.6)	12 (11.1)	0.318
Treatment Parameters			
Total atropine dose (mg), mean ± SD	186.4 ± 98.2	78.6 ± 52.4	<0.001
Inadequate atropinization, n (%)	22 (64.7)	31 (28.7)	<0.001
Pralidoxime administered, n (%)	28 (82.4)	84 (77.8)	0.566
Pralidoxime within 12 hours, n (%)	16 (47.1)	72 (66.7)	0.042
Mechanical ventilation required, n (%)	23 (67.6)	12 (11.1)	<0.001
ICU length of stay (days), mean ± SD	12.4 ± 6.8	4.2 ± 2.6	<0.001

Multivariate Analysis: Multivariate logistic regression analysis identified estimated quantity ingested >50 mL (OR=3.42; 95% CI: 1.87-6.24; p<0.001), inadequate atropinization (OR=4.18; 95% CI: 2.11-8.27; p<0.001), admission

cholinesterase <500 U/L (OR=2.89; 95% CI: 1.56-5.35; p=0.001), and delayed presentation >6 hours (OR=2.24; 95% CI: 1.18-4.26; p=0.014) as independent predictors of IMS development.

Outcomes: Mortality in the IMS group was significantly higher (23.5% vs. 4.6%; p<0.001). Among survivors, complete recovery was observed in 24 of 26 IMS patients (92.3%) at 3-month follow-up.

Discussion

The present study identified an IMS incidence of 23.9% among patients with acute OP poisoning, which aligns with previously reported rates of 20-40% in similar hospital-based studies [13]. The identification of modifiable risk factors, particularly inadequate atropinization and delayed presentation, provides opportunities for intervention to reduce IMS incidence. The strong association between low admission cholinesterase levels and IMS development corroborates previous findings suggesting that the degree of enzyme inhibition reflects poisoning severity and predicts complications [14]. The threshold of 500 U/L identified in our study as a significant predictor is consistent with observations by Jayawardane et al., who reported similar cut-off values for predicting respiratory failure [15].

Our finding that dimethyl compounds confer higher IMS risk compared to diethyl compounds supports the hypothesis that the fat solubility and tissue distribution patterns of different OP compounds influence their neuromuscular effects [16]. Dimethyl compounds, including monocrotophos and dimethoate, are known to cause more prolonged receptor occupation and slower enzyme reactivation [17]. The critical role of adequate atropinization in preventing IMS represents a potentially modifiable factor. While atropine primarily addresses muscarinic effects, adequate early atropinization may prevent secondary hypoxic damage to neuromuscular junctions and reduce overall oxidative stress [18]. The finding that inadequate atropinization increased IMS risk four-fold underscores the importance of aggressive initial management. Delayed presentation emerged as an independent predictor, likely reflecting prolonged toxin exposure before treatment initiation. This finding has important public health implications, particularly in rural areas where access to healthcare facilities is limited [19]. Strategies to reduce time to treatment, including community-based first aid training and improved transportation, may help reduce IMS incidence. The higher mortality observed in the IMS group (23.5% vs. 4.6%) emphasizes the clinical significance of this complication. Similar mortality rates have been reported in other Asian studies, ranging from 15% to 40% [20]. The requirement for prolonged mechanical ventilation in IMS patients increases the risk of ventilator-associated complications and contributes to poor outcomes. Interestingly, pralidoxime administration itself was not protective against IMS in our study, consistent with recent randomized controlled trials questioning its efficacy [21]. However, early pralidoxime administration (within 12 hours) showed a trend toward reduced IMS incidence, suggesting that timing may be more important than administration per se [22]. The study has several limitations. The single-center design may limit generalizability. Compound identification relied primarily on history, as container examination was not always possible. Additionally, the grading of IMS severity was not systematically performed, precluding analysis of factors associated with severe IMS.

Conclusion

This study demonstrates that intermediate syndrome develops in approximately one-quarter of patients with acute organophosphorus poisoning and is associated with significantly increased morbidity and mortality. Key determinants include the quantity of compound ingested, type of OP compound (dimethyl versus diethyl), degree of cholinesterase inhibition at presentation, delayed presentation to healthcare facilities, and adequacy of initial atropinization. These findings have important clinical implications. Patients presenting with severely depressed cholinesterase levels, large ingestion quantities, or delayed presentation should be identified as high-risk and monitored closely for IMS development. Ensuring adequate early atropinization and reducing time to treatment initiation represent potentially modifiable factors that may reduce IMS incidence. Implementation of these evidence-based strategies in clinical practice could improve outcomes in this vulnerable patient population.

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