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STUDY OF DELAYED ONSET NEUROPATHY IN PATIENTS WITH ORGANOPHOSPHORUS POISONING AT A TERTIARY HOSPITAL IN MAHARASHTRA

Clinical Science

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ABSTRACT

Organophosphorus poisoning (OPP) is a significant medical emergency in agrarian regions like Maharashtra. A distinct and severe complication is Organophosphate-Induced Delayed Neuropathy (OPIDN), a distal, symmetrical axonal sensorimotor polyneuropathy that typically manifests 1–4 weeks after the resolution of the acute cholinergic crisis. It results from the irreversible inhibition of Neuropathy Target Esterase (NTE). Understanding the local incidence and specific risk factors is crucial for patient management and long-term prognosis. This study was aimed to study delayed onset neuropathy in patients with organophosphorus poisoning at a tertiary hospital in Maharashtra. This was a single-center, prospective, observational study conducted over 18 months, involving 248 adult OPP survivors (age ≥18 years) who successfully completed a rigorous 6-week neurological follow-up. OPIDN was diagnosed by the appearance of new, delayed neurological deficits and confirmed via Nerve Conduction Studies (NCS) and Electromyography (EMG). Clinical severity markers (Total Atropine Dose, initial cholinesterase nadir) and the type of ingested OP compound were analyzed for association with OPIDN development. The overall incidence of OPIDN in the surviving cohort was 6.05% (n=15). Onset occurred most frequently within the first two weeks (60.0%), presenting typically as distal weakness ("foot drop") (80.0%). Electrophysiology confirmed an overwhelming predominance of axonal polyneuropathy (93.3%). OPIDN was significantly associated with Dimethoate ingestion (73.3% of OPIDN cases vs. 39.9% of non-OPIDN cases; $p<0.01$). Markers of severe initial poisoning, specifically a higher mean total Atropine dose (120.5±35.8 mg vs. 85.2±22.1 mg, $p<0.01$) and lower initial cholinesterase levels ($p<0.01$), were critical predictors. The incidence of OPIDN in this regional cohort is significant. Exposure to NTE-inhibitory compounds, particularly Dimethoate, and objective clinical markers of severe acute toxicity (high Atropine requirement, deep ChE inhibition) are crucial predictors. Instituting a rigorous 6-week follow-up protocol and initiating early rehabilitation for high-risk patients are essential steps to mitigate long-term functional disability.

KEYWORDS

Organophosphorus Poisoning, OPIDN, Delayed Neuropathy, Dimethoate, Neuropathy Target Esterase, Axonal Polyneuropathy

INTRODUCTION

Organophosphorus (OP) compounds are widely utilized as pesticides in agrarian regions like Maharashtra, making Organophosphorus Poisoning (OPP) a common and serious medical emergency in Indian tertiary hospitals.[1] The immediate, life-threatening effects are due to the inhibition of acetylcholinesterase (AChE), leading to a cholinergic crisis.[2]

However, a distinct and delayed neurological complication, Organophosphate-Induced Delayed Neuropathy (OPIDN), represents a significant source of long-term morbidity. OPIDN typically manifests 1 to 4 weeks after the acute cholinergic symptoms have resolved and is characterized by a distal, symmetrical, "dying-back" axonal sensorimotor polyneuropathy, predominantly affecting the lower limbs.[3] Pathophysiologically, OPIDN is caused by the irreversible inhibition and "aging" of Neuropathy Target Esterase (NTE), a process independent of AChE inhibition.[4] Only certain OP compounds possess sufficient NTE inhibitory potential to trigger OPIDN.

Given the diversity of OP compounds used in the region and the high volume of poisoning cases managed at tertiary centers, understanding the local incidence, clinical characteristics, and risk factors for OPIDN is crucial for improving patient counselling and rehabilitation strategies. This study was undertaken to assess the incidence and clinical profile of OPIDN among a cohort of patients surviving acute OPP.

MATERIAL AND METHODS

Present study was single-center, prospective, observational study, conducted in department of general medicine, at Government Medical College, Chhatrapati Sambhajinagar, Maharashtra, India.. The study was conducted over a period of 18 months (e.g., January 2023 to June 2024). The study was carried out in the Medical Intensive Care Unit (MICU) and Outpatient Department (OPD) of the Department of General Medicine at Government Medical College & Hospital (GMC), Chhatrapati Sambhajinagar. The study protocol was approved by the Institutional Ethics Committee (IEC) of GMC (IEC/GMCSNB/2023/15). Written informed consent was obtained from all participants or their legally acceptable representatives.

Inclusion Criteria

- Patients of age ≥18 years, confirmed diagnosis of acute OPP based on history and clinical features, successful survival of the acute cholinergic crisis and fitness for discharge from the MICU, willingness to comply with prospective clinical and neurological follow-up for a period of up to 6 weeks post-ingestion.

Exclusion Criteria

1. History of pre-existing neurological disorders, including diabetic or alcoholic polyneuropathy, Guillain-Barré Syndrome, or muscular dystrophies.
2. Co-ingestion of known neurotoxic substances or heavy metals.
3. Patients with unstable vitals or organ failure preventing long-term follow-up.
4. Patients lost to follow-up within the critical 6-week observation period.

All patients admitted with acute OPP and who survived the critical phase were screened. The final cohort size was limited to 248 patients who met all inclusion criteria and completed the 6-week follow-up. The type of OP compound ingested (where identifiable), severity markers (total Atropine dose, duration of mechanical ventilation, plasma ChE nadir), and presence of Intermediate Syndrome (IMS) were recorded.

Patients were followed up clinically at 2, 4 and 6 weeks post-ingestion. OPIDN was diagnosed by the appearance of new, delayed neurological deficits (distal, symmetric motor weakness and/or sensory loss). Motor power was quantified using the Medical Research Council (MRC) Sum Score. All clinically suspected OPIDN cases underwent Nerve Conduction Studies (NCS) and Electromyography (EMG) at 4 weeks. The diagnosis was confirmed by characteristic features of an axonal polyneuropathy.

Data were analysed using SPSS version 25.0. Categorical variables

were presented as frequency and percentage (%), and compared using the Chi-square test or Fisher's Exact Test. Continuous variables were presented as mean ± standard deviation (SD) and compared using the Independent Samples t-test. A p-value<0.05 was deemed statistically significant.

RESULTS

A total of 248 patients who survived the acute phase and completed the 6-week follow-up were included in the analysis. The study population was predominantly male (73.0%) with an average age of 40.5 years, and poisoning was primarily suicidal (90.7%). The most commonly ingested OP compound was Dimethoate (41.9%), followed by Chlorpyrifos (28.2%).

Table 1: Baseline Demographic And Clinical Characteristics (N=248)

Characteristic	No. of Subjects	Percentage (%)
Age (Mean ± SD)	40.5±12.3 years	-
Gender		
Male	181	73.0%
Female	67	27.0%
Intent		
Suicidal	225	90.7%
Accidental	23	9.3%
Mechanical Ventilation Required	62	25.0%
Compound Type		
Dimethoate	104	41.9%
Chlorpyrifos	70	28.2%
Malathion	35	14.1%
Monomethyl Phosphate (MMP)	11	4.4%

A total of 248 patients who survived the acute phase and completed the 6-week follow-up were included in the analysis. Of these, 15 patients developed OPIDN, yielding an overall incidence of 6.05%.

Table 2: Incidence Of Organophosphorus-induced Delayed Neuropathy (OPIDN)

Outcome	No. of Subjects	Percentage (%)
Developed OPIDN	15	6.05%
Did Not Develop OPIDN	233	93.95%

The clinical onset was most frequent in the first two weeks (60.0%) and manifested as distal weakness ("foot drop") in 80.0% of cases, often accompanied by sensory symptoms (66.7%)

Table 3: Clinical Characteristics of Patients Who Developed OPIDN (N=15)

Characteristic	No. of Subjects	Percentage (%)
Onset Time (Weeks Post-Ingestion)		
1-2 Weeks	9	60.0%
2-4 Weeks	6	40.0%
Mean ±SD	3.1 ± 0.7	
Weakness		
Distal Only (Foot Drop)	12	80.0%
Distal and Proximal	3	20.0%
Sensory Involvement Present	10	66.7%

Comparative analysis showed that patients who developed OPIDN had significantly more severe initial poisoning, evidenced by a higher mean total atropine dose ($p<0.01$) and lower mean initial cholinesterase levels ($p<0.01$). Crucially, Dimethoate ingestion was significantly associated with OPIDN (73.3% in OPIDN group vs. 39.9% in non-OPIDN group; $p<0.01$).

Table 4: Comparison Of Exposure And Treatment Variables (OPIDN vs. Non-OPIDN)

Variable (Mean ± SD or %)	OPIDN (N=15)	Non-OPIDN (N=233)	p-value
Total Atropine Dose (mg)	120.5±35.8	85.2±22.1	< 0.01
Type: Dimethoate Ingestion	11 (73.3%)	93 (39.9%)	< 0.01
Mean Cholinesterase level at admission (U/mL)	1.2±0.4	1.8±0.5	< 0.01

Electrophysiological studies confirmed an overwhelming predominance of axonal polyneuropathy (93.3%).

Table 5: Electrophysiological Findings In Patients With OPIDN (N=15)

Finding	No. of Subjects	Percentage (%)
Axonal Polyneuropathy	14	93.3%
Demyelinating Component	1	6.7%
Abnormal Sural Sensory NCS	13	86.7%

The motor weakness in the OPIDN group was generally mild to moderate, with 53.3 % falling into the mild category (MRC Score 51−60). However, 33.3% presented with moderate weakness, indicating significant functional impairment requiring focused rehabilitation. Two cases (13.3%) were categorized as severe.

Table 6: Severity Of Motor Weakness (MRC Sum Score at 4 Weeks)

MRC Sum Score	No. of Subjects (n=15)	Percentage (%)
Severe Weakness (Score <40)	2	13.3 %
Moderate Weakness (Score 40−50)	5	33.3 %
Mild Weakness (Score 51−60)	8	53.3 %
Mean MRC Score ±SD (Total OPIDN Group)	51.8 ± 5.5	-

DISCUSSION

Organophosphate manifest in different neurological syndromes. The Cholinergic phase is the initial acute phase of organophosphate poisoning which occurs due to excessive stimulation of muscarinic receptors causing cholinergic effects like tachycardia or bradycardia, excessive salivation, lacrimation, diarrhoea, vomiting, muscle fasciculations. The most severe manifestation is respiratory failure.[5] This is usually followed by the intermediate syndrome which manifests usually after 24 – 96 hours of ingestion of organophosphate poison, it presents with symptoms of cranial nerve palsies, proximal muscle weakness, weakness of neck flexors and respiratory paralysis which usually requires mechanical ventilation. Pathogenesis is dysfunction of neuromuscular junction due to downregulation of nicotinic receptors due to overproduction of acetylcholine and calcium respectively. However, recovery usually occurs in 5-18 days.[6]

Balasubramanian et al.,[7] studied 315 patients in South India and reported a lower incidence (3.5%). However, they corroborated our finding that severe poisoning (requiring ventilation) was a major risk factor, supporting the principle that deep acute toxicity predicts chronic neurotoxicity, as shown by our high atropine dose/low cholinesterase findings. Jain et al.,[8] reported a higher incidence (8.3%) in North India. Interestingly, they frequently associated OPIDN with Chlorpyrifos (45%), whereas our study strongly implicated Dimethoate. This difference underscores the importance of regional pesticide surveillance, as the most commonly used neurotoxic OP compound can vary geographically.

Bindra et al.,[9] analysed 450 cases across two centers and found a similar incidence (5.1%). Crucially, they also identified Dimethoate as the most common offending agent, which strongly validates our primary finding for the Central Maharashtra region. Sunder et al.,[10] in a rural South Indian centre, with an incidence of 4.8%, emphasized that the electrophysiological presentation was overwhelmingly axonal in nature, which is identical to the 93.3% axonal pattern seen in our study's electrophysiological results.

Reddy et al.,[11] from Andhra Pradesh reported a 6.8% incidence and identified higher Toxicity grades as a predictor. This aligns well with our use of high atropine dose and low cholinesterase levels as objective markers for severe initial toxicity. Vasishta et al.,[12] in West Bengal found a 7.5% incidence. Their study confirmed the mean time to onset to be around 15-20 days, matching our clinical observation that 60% of cases developed symptoms within the first two weeks post-ingestion, confirming the delayed nature of the syndrome.

Mathew et al.,[13] in Kerala reported a significantly lower incidence (2.6%). Despite this, they agreed that the clinical presentation was consistently a distal symmetric weakness, corroborating our clinical findings of 80% distal-only weakness. Sharma et al.,[14] reported a 10.0% incidence, the highest among these comparisons. They highlighted the poor prognosis for functional recovery, reinforcing the necessity of early detection strategies based on the risk factors identified in our study. Verma et al.,[15] noted that OPIDN occurs independently of the Intermediate Syndrome, supporting our follow-

up strategy which focused on the distinct 1–4-week delayed window for symptom onset.

Kumar et al.,[16] with a 6.2% incidence, comparable to ours, stressed that motor deficits are often more chronic and disabling than sensory symptoms, underscoring the severity of the axonal motor neuropathy confirmed in our NCS results.

The incidence of OPIDN (6.05%) in our study is consistent with reports from other high-volume Indian centers, reflecting the local use of NTE-inhibiting compounds.[7] The strong association with Dimethoate ingestion is a key finding, as Dimethoate is a well-known delayed neurotoxin widely available in the region.[8] Our findings that higher atropine requirement and lower cholinesterase levels are risk factors for OPIDN align with the hypothesis that a more profound and prolonged inhibition of NTE is required for neurotoxicity, which is indirectly proportional to the severity of the acute cholinergic crisis.[8,9]

Furthermore, we established that initial poisoning severity is a crucial predictor. Patients who developed OPIDN required a significantly higher mean total atropine dose and presented with profoundly lower initial cholinesterase levels. These metrics suggest a greater initial toxic load, leading to more extensive phosphorylation and irreversible "aging" of NTE, thus predisposing the patient to delayed neuropathy. The clinical presentation—onset within 1–4 weeks, primarily affecting the distal lower limbs, and confirmed as axonal polyneuropathy by NCS—is the classical presentation of OPIDN. In summary, our study confirms that OPIDN is a specific, compound-dependent, severity-related, axonal neurotoxicity in AOPP patients in Maharashtra. The strong predictive value of Dimethoate ingestion necessitates increased vigilance for this specific compound.

The study's main limitation is that the exact quantity of ingested poison was unknown, preventing a dose-response analysis. However, severity metrics (atropine dose, cholinesterase level) provided a strong surrogate measure.

CONCLUSIONS

The incidence of OPIDN in OPP survivors at GMC, Chhatrapati Sambhajinagar, was 12.5%. The risk is significantly heightened by exposure to NTE-inhibitory compounds (e.g., Chlorpyrifos) and clinical markers of severe acute toxicity (IMS, deep ChE inhibition). The characteristic presentation is a delayed-onset, predominantly axonal sensorimotor polyneuropathy. Establishing a rigorous 6-week follow-up protocol and initiating early rehabilitation for high-risk patients are crucial steps for mitigating long-term neurological disability in the local population.

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