ORIGINAL ARTICLE

Prognostication and Prediction of Outcomes in Patients with Organophosphorus and Carbamate Poisoning: A Prospective Cohort Study

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Abstract

Background: Organophosphorus (OP) and carbamate poisoning are significant concerns in developing nations. This study evaluates the effectiveness of the ChE check mobile, a cholinesterase-rapid bedside diagnostic test, in the diagnosis and management of OP and carbamate poisoning.

Materials and methods: We conducted this prospective observational study, involving patients with OP and carbamate poisoning over 1 year (June 2016 to June 2017) at a single tertiary care center. Levels of RBC cholinesterase (E-AChE), butyl cholinesterase (BChE), and various other determinants were systematically coded and analyzed.

Results: The study population ($n = 60$) consisted primarily of males ($n = 43$; 71.7%), with a mean age of 30.6 (SD: 13.7) years. Monocrotophos ($n = 10$; 20.4%) and carbofuran ($n = 4$; 8.1%) were the commonest OP and carbamate compounds, respectively. The median initial atropinization dose was 10 (*IQR*: 0, 61.5) mg, with a median total administered atropine dose of 116 (IQR: 32, 320) mg. A significant negative correlation was found between E-AChE levels and both the initial atropinization dose (ρ: –0.653, p-value < 0.001) and total atropine requirement (ρ: –0.659, p-value < 0.001) during admission. An E-AChE cut-off of 4 units/g hemoglobin provided an area under the curve of 0.73 (sensitivity: 80.0%, specificity: 68.6%, p-value < 0.001) for predicting moderate to severe peradeniya organophosphorus poisoning.

Conclusion: The check mobile device can be a valuable tool for prognosticating patients. There was a significant correlation between low E-AChE levels and the atropine requirement and severity.

Keywords: Acetylcholinesterase, Carbamate poisoning, ChE check mobile, Organophosphorus poisoning, Pseudocholinesterase, RBC cholinesterase.

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Highlights

This study utilized a handheld device to assess E-AChE (erythrocyte acetylcholinesterase) levels and established a robust link with poisoning severity. Plasma BChE (butyrylcholinesterase) levels showed no such correlation. The findings underscore the necessity for customized treatment based on poisoning severity and emphasize the importance of careful atropine administration. Our study reports a lower mortality rate attributed to well-equipped healthcare facilities.

Introduction

Organophosphorus (OP) and carbamate poisoning pose a significant public health challenge, particularly in countries like India where agriculture is one of the largest economic sectors.[1–3] These instances of poisoning constitute a significant share, approximately estimated to range from 1 to 2%, among cases presenting to the emergency room (ER).[4–6] In our institution, OP and carbamate poisoning frequently necessitate admissions to the high dependency unit (HDU) and intensive care unit (ICU), mirroring the situation in other healthcare facilities.[7,8] The toxicity of OP and carbamate poisoning stems from their capacity to deactivate the enzyme acetylcholinesterase, leading to the accumulation of acetylcholine and subsequent overstimulation of receptors.[9–11] Serious clinical manifestations of both OP and carbamate poisoning share similarities. Delayed or inadequate treatment can result in severe consequences such as muscle paralysis, cardiac brady-asystole, secretory gland hypersecretion, respiratory failure, coma, and even fatality. Timely administration

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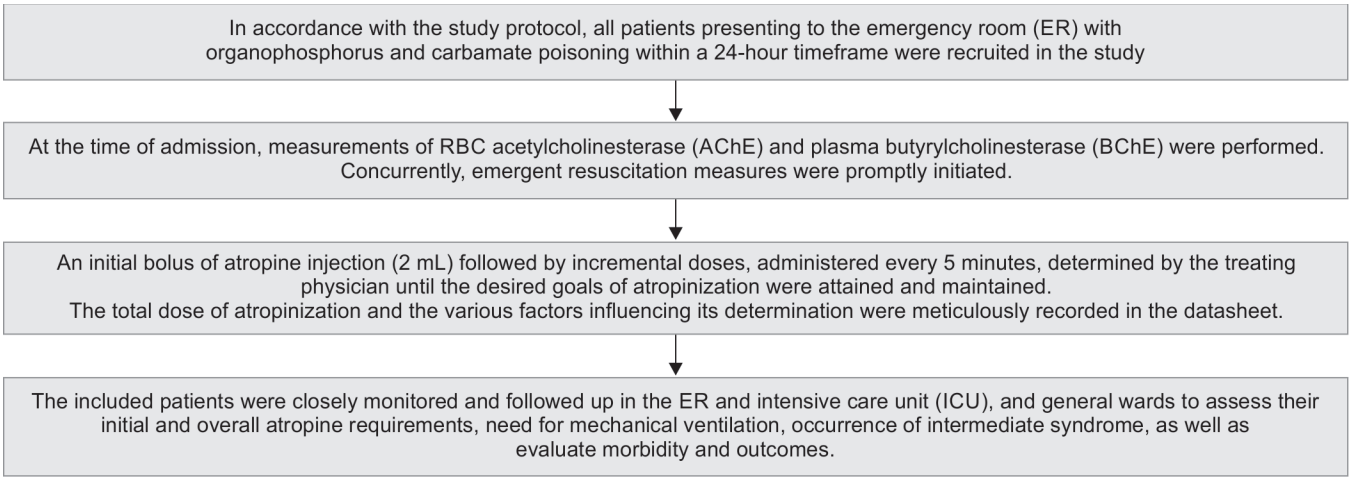

Fig. 1: Consolidated standards of reporting trials (CONSORT) diagram

of antidotes significantly reduces the clinical severity of poisoning and eliminates symptoms.[2,6,10–12]

The OP compounds not only have a high affinity for synaptic acetylcholinesterase (S-AChE) but also lead to the inhibition of various other cholinesterases, including red blood cell or erythrocyte cholinesterase (E-AChE) and butyl cholinesterase (BChE) (also known as pseudo-cholinesterase). Direct measurement of S-AChE is not feasible; thus, we depend on surrogate markers such as E-AChE or pseudocholinesterase levels.[9,11] Notably, many OP substances exhibit stronger inhibitory effects on BChE compared to AChE, resulting in lower-than-expected BChE levels in clinical settings.[13] Several laboratory methods, including the most popular Ellman et al.'s method, have been developed to assess E-AChE levels.[14–16] Field-testing kits, such as the Test-mate ChE system and Lovibond Cholinesterase AF 267 test kit, are available for E-AChE or BChE testing using the Ellman method.[17–20] While BChE levels are commonly used in diagnosing OP poisoning, their correlation with clinical severity remains limited.[2,11,13,14] Conversely, E-AChE, although not routinely utilized, may exhibit a stronger correlation due to its structural similarity to the synaptic cholinesterase enzyme.

In this study, we used the ChE check mobile, a cholinesterase rapid test *in vitro* diagnostic (IVD) device, that works through Ellman's colorimetric principle to estimate E-AChE levels and evaluate its correlation with poisoning severity, atropine requirements, and prognosis.

Materials and Methods

Study Setting

A large tertiary care referral hospital in Tamil Nadu, South India.

Study Period

The study was conducted over 1 year, from June 1, 2016, to June 30, 2017.

Participants

Inclusion Criteria

Consecutive adult patients (age ≥18) presenting to the ER with cholinergic toxidrome or evidence of OP or carbamate ingestion in the form of a bottle of the chemical or its photograph from the scene presenting presumably within 24 h from ingestion were included in the study.

Exclusion Criteria

Patients who were brought in dead after OP or carbamate ingestion, those with unknown poisoning with no classical cholinergic toxidrome, pregnant women and those who declined to provide written consent were excluded.

Sample Size

Due to the lack of larger studies that establish a correlation between E-AChE levels, poisoning severity, or atropine requirements, all consecutive cases of OP or carbamate poisoning meeting the inclusion criteria during the 12-month study period were included.

Estimation of E-AChE and Plasma BChE Levels

E-AChE levels were measured using Rapid ChE Check Mobile, while plasma BChE activity was determined using conventional laboratory techniques.[18–20] These tests were performed at the patient's presentation to the ER. However, the results of E-AChE levels were not disclosed to the ER physicians to ensure that the management protocol remained unaffected. Laboratory plasma BChE levels were estimated using the modified Ellman's method which produces a specific colour.[16,19] The intensity of the resulting color is measured using a spectrophotometer, and this measurement is used to express the value of cholinesterase levels.[19] The RBC AChE levels were assessed using the rapid ChE check mobile, a device developed by the Bundeswehr Institute of Toxicology and Pharmacology.[21] Blood samples were collected in EDTA tubes (2 mL), and 10 microliters of blood were drawn into a capillary tube (included with the device) for the estimation of E-AChE using a modified Ellman method. The results could be obtained within 5 min, and the device does not have any significant technical requirements. As per the manufacturer's claims, this device exhibited a strong correlation (*r*-value of 0.93) with laboratory values obtained through the Ellman method, based on 10 samples for AChE.[21]

Variables

Demographic and baseline characteristics, including the ingested substance, vital signs, signs and symptoms at presentation, history of prior medical care, the time interval between ingestion and presentation, presenting complaints, E-AChE in units per

gram hemoglobin, and plasma BChE levels in units per liter, and laboratory findings, were recorded (Fig. 1). Additionally, atropine toxicity, intermediate syndrome, length of hospital stays, mechanical ventilation requirements, inotropic use, duration of HDU or ICU stay, concomitant illness, and mortality were also noted.

Emergency Room Management

Patients were managed by evidence-based ER guidelines and protocols. Injection atropine bolus/infusion was used to achieve the goals of atropinization based on the clinical judgment of the attending ER physicians, following the definitions outlined in a review article published by Eddleston et al.[22] Due to the unproven benefits of oximes in meta-analyses and potential risks, they were not used.[23] To assess the potential occurrence of atropine toxicities and the need for physical and chemical restraints, we used the confusion assessment method (CAM).[24] For a diagnosis of delirium by CAM, the patient must display a presence of acute onset and fluctuating discourse and inattention with either disorganized thinking or an altered level of consciousness which was assessed by the principal investigator daily once from the day of admission in the hospital till discharge.

Data Source and Statistical Analysis

Data were initially entered in Microsoft Excel version 16.65, and subsequent statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows (IBM Corp. Released 2017, Version 25.0, Armonk, NY, USA). Outliers and extreme values were checked using the Box-Cox plot and histogram. Summary statistics were used to report demographic and clinical characteristics. The *t*-test was used for continuous data with a normal distribution, while the Mann–Whitney *U* test was used for data with a non-normal distribution. The Chi-square test was applied for categorical variables. Spearman's correlation analysis was employed to assess the strength and direction of association between two sets of ranked variables. ANOVA analysis was done for assessing the variance of means between multiple groups. All statistical significance was predefined as a *p*-value less than 0.05.

Results

A total of 60 patients meeting the predefined inclusion criteria were enrolled in the study. The mean age of the study population was 30.6 (SD: 13.7) years, with a predominance of male patients ($n = 43$; 71.7%). The vital signs and symptoms observed at the presentation are provided in Table 1. The severity of poisoning was assessed using the peradeniya organophosphorus poisoning (POP) scale, a validated scale for assessing the severity of OP poisoning, and the results are presented in Table 1.[25–27]

Monocrotophos ($n = 10$; 20.4%) and Carbofuran ($n = 4$; 8.1%) were the most commonly ingested OP and carbamate compounds, respectively. Out of the 49 cases analyzed, compounds were detected in 25 (51.0%) cases belonging to WHO class I, 23 (46.9%) cases in class II, and 1 (2.1%) case in class III. Additional details regarding the toxicants ingested and the toxidrome observed at the presentation can be found in Table 2. It is worth noting that two patients had also consumed drugs (Alprazolam and Imidacloprid) alongside the toxic substances. Most patients ($n = 50$, 83.3%) had received primary medical care from another facility before presenting to our center. The care received included gastric lavage ($n = 43$; 71.7%), a bolus dose of injection atropine ($n = 36$; 60.0%), induced emesis using salt ($n = 12$; 20.0%), administration of oximes ($n = 6$; 10.0%), intubation and mechanical ventilation ($n = 4$; 6.7%).

Table 1: Vital signs/symptoms and peradeniya organophosphorus poisoning (POP) severity scale at presentation to the emergency room[25–27]

Vital signs	*Frequency (%)*
Pulse rate per minute: mean (SD#)	104 (27.63)
Systolic blood pressure in mm Hg: mean (SD#)	112 (28.1)
Respiratory rate per minute: mean (SD#)	23.5 (8.3)
Signs at presentation	
GCS* <8 (Very drowsy/not obeying commands/ mild response to painful stimuli)	18 (30.5)
GCS* 8–12 (Drowsy/not obeying commands/ responding to painful stimuli)	3 (5.1)
GCS* ≥13 (Normal or near-normal sensorium)	39 (64.4)
General random blood sugar (SD#) mg/dL	140.65 (63.94)
Constricted pupil (<2 mm)	29 (49.2)
Diaphoresis	21 (35.6)
Lung crepitations	25 (41.7)
Salivation	25 (41.7)
Frothing	17 (28.3)
Fever	2 (3.3)
Fasciculation	13 (21.7)
Abdominal tenderness	4 (6.7)
Paradoxical breathing	16 (27.1)
Peradeniya organophosphorus poisoning (POP) scale	
Mild	35 (58.3)
Moderate	22 (36.7)
Severe	3 (5)

SD#, standard deviation; GCS*, Glasgow Coma Scale

The details of the ER and ICU management, complications, and outcomes are summarized in Table 3. The study findings revealed that the median E-AChE level was 4 (IQR: 1.3, 18.8) units/gram hemoglobin, and the median plasma BChE was 175 (IQR: 96, 2013) units per liter. The initial median dose of atropine required for atropinization was 10 mg (IQR: 0, 61.5), and the median total atropine dose administered was 116 (IQR: 32, 320) mg. On average, patients required atropine treatment for 2.7 (SD: 1.7) days. The E-AChE level showed a significant negative correlation with both the initial atropinization dose (Spearman's rho or ρ: −0.653, p-value < 0.001) and the total atropine requirement (ρ: −0.659, p-value < 0.001) during admission, serving as a predictor of various measures of severity, as outlined in Table 4. However, the concurrently measured plasma BChE did not demonstrate any significant correlation with atropine requirements (p-value: 0.12), ICU admission (p-value: 0.07), or severity of poisoning based on POP (p-value: 0.056). Both E-AChE and plasma BChE were found to predict in-hospital mortality (p-value: 0.002). Approximately, one-third of the patients ($n = 22$; 33.6%) developed atropine delirium and required restraint measures. Patients with delirium had a significantly higher median total atropine dose [72 (IQR: 32, 325.5) mg] compared to those without atropine-related adverse effects [28 (IQR: 0, 121) mg] (p-value: 0.038).

Among the entire sample, 55% ($n = 33$) of the patients necessitated mechanical ventilation and were subsequently admitted to the medical ICU. The main reasons for intubation in

Table 2: Ingested toxicants and toxidrome of patients presenting to the emergency room with organophosphorus and carbamate poisoning

Variables	*Frequency 60 (%)*
Identifiable compound(s)*	49 (81.7)
Monocrotophos (OP#)	10 (20.4)
Chlorpyrifos (OP#)	9 (18.4)
Phorate (OP#)	8 (16.3)
Profenofos (OP#)	6 (12.3)
Triazohphos (OP#)	1 (2.04)
Dimethoate (OP#)	2 (4.1)
Dichlorvos (OP#)	2 (4.1)
Quinalphos (OP#)	1 (2.04)
Malathion (OP#)	1 (2.04)
OP# compounds + cypermethrin (pyrethroid compound)	5 (10.2)
Diethyl organophosphorus compounds	19 (38.8)
Dimethyl organophosphorus compounds	26 (53.1)
Carbofuran (carbamate poison)	4 (8.1)

Identifiable compound(s)*: Identified by the bottle or leaflet of the pesticide or as told by the relatives (confirmed with the bottle/leaflet picture on the phone). The remaining cases were diagnosed based on the clinical features or typical toxidrome of Organophosphorus/carbamate poisoning. OP#, organophosphorus compounds

Table 3: Management of patients in the emergency room, details related to injection atropine administration, intensive care unit-related details, associated complications, and the overall hospital outcome

Emergency room management-related details	*Frequency (%)*
Decontamination	60 (100.0)
Gastric lavage	10 (16.7)
Activated charcoal	4 (6.7)
Intubation and mechanical ventilation	14 (23.3)
Supportive care (Intravenous fluids/ antiemetics/proton-pump inhibitors, etc.)	49 (81.7)
Inotropes	0 (0.0)
Injection atropine-related details	*Median (IQR#)*
Initial atropinization dose (mg)	10 (0, 61.5)
Total atropine dose (mg)	116 (32, 320)
Duration of atropine infusion in days	2 (2, 3)
Atropine delirium: *n* (%)	22 (33.6)
Hospitalization details	*Frequency (%)*
Admission to the intensive care unit (ICU)	33 (55.0)
Intubation and mechanical ventilation either in another medical center, in the ER! or after admission (total)	33 (55.0)
Duration of mechanical ventilation in days – median (IQR#)	7.5 (3.75, 14.25)
Required tracheostomy for prolonged ventilatory support	14 (23.3)
Intermediate syndrome (IMS)	18 (30.0)
Duration of intermediate syndrome in days – median (IQR#)	8.5 (5, 11.75)
Hospital outcome	*Frequency (%)*
The total duration of admission in the hospital – median (IQR#)	6 (4, 13)
Discharged stable	53 (88.3)
Discharged against medical advice	4 (6.7)
Died in hospital	3 (5.0)
Probable cause for death	*Frequency (%)*
Cholinergic crisis	1 (1.66)
Ventilator-associated pneumonia	1 (1.66)
Sepsis – bacteremia	1 (1.66)

ER!, emergency room; IQR#, interquartile range

the ER were primarily attributed to low sensorium and respiratory failure, accounting for 23.3% ($n = 14$) of cases. Additionally, 15 patients had to be intubated after their admission to the hospital. Among patients experiencing acute cholinergic crises, ventilatory support could be discontinued within 5 days. However, prolonged ventilatory support was needed for patients who developed hospital-acquired infections or intermediate syndrome. In the ICU, three patients succumbed to their illness, one due to acute cholinergic crises, while the others were infection-related (Table 3). The E-AChE levels in the three fatal cases were recorded as 0, 2.4, and 2 U/g Hb, contrasting with a median (IQR) of 4.1 (1.3–4.1) U/g Hb in other cases. During hospitalisation, 23 patients (38.3%) acquired infections. Among these, there were 21 cases of ventilator-associated pneumonia, 2 cases of urinary tract infection, and 5 cases of blood culture-proven bacteremia.

When studying atropine requirements for initial treatment and outcomes in various severity levels of OP poisoning using the POP scale, significant differences were found in the median (range) of initial atropinization doses: mild group: 0 (0–64) mg, moderate group: 31.5 (0–256) mg, and severe group: 81 (60–222) mg. The severity of OP poisoning was directly linked to ventilation needs. All patients in the severe group required ventilation, while a significantly higher proportion of patients in the moderate group (90.9%) needed respiratory support compared to the mild group (28.6%). ICU admission rates followed a similar pattern, further emphasizing the importance of early patient classification and referral at smaller healthcare centers.

A receiver operating characteristic (ROC) curve was plotted to determine the optimal cut-off value for E-AChE in predicting moderate to severe poisoning according to the POP scale (Fig. 2). On the other hand, the institutional lower limit of pseudocholinesterase or BChE at 5320 U/L had a higher sensitivity of 92% but a poor specificity of 20.6% for predicting moderate to severe poisoning according to the POP scale. In addition, a ROC curve was plotted for the optimal cut-off of plasma BChE (Fig. 3).

Discussion

The ingestion of OP and carbamate poisons is a common method of intentional self-harm observed in our ER.[6,8] The current gold standard for diagnosing anticholinesterase poisoning in most medical centers involves measuring pseudo-cholinesterase levels.[2,16] However, the literature review revealed a minimal correlation between BChE levels and clinical severity or patient outcomes.[15–17] In contrast, a study by Thiermann et al. demonstrated that RBC cholinesterase or E-AChE correlated with neuromuscular weakness.[28] Building upon this knowledge, our study measured E-AChE using a handheld cholinesterase check device at admission and examined the link between severity and outcomes. In resource-limited settings in India and other developing countries,

Table 4: Correlation between RBC cholinesterase (E-AChE) levels and the prognosis of organophosphorus and carbamate poisoning

Variables	*Measure of association*	*p-value*
RBC cholinesterase levels in units/gram hemoglobin		
The initial dose of atropine (mg)	ρ: –0.653	<0.001
The total dose of atropine (mg)	ρ: –0.659	<0.001
Admission in Intensive Care Unit: median (IQR[#]) of RBC cholinesterase		
Yes	1.8 (IQR: 0.9, 6.1)	0.002
No	14.9 (IQR: 3.7, 40.1)	
Moderate to severe POP% severity scale: median (IQR[#]) of RBC cholinesterase		
Yes	1.6 (IQR: 0.65, 3.75)	0.001
No	8.45 (IQR: 1.93, 37.75)	
Duration of hospital stay	ρ: –0.302	0.02
Intermediate syndrome: median (IQR[#]) of RBC cholinesterase		
Yes	1.65 (IQR: 0.75, 6.95)	0.06
No	4.1 (IQR: 1.6, 35.35)	

ρ: rho-value – Spearman's coefficient of correlation; POP[%], peradeniya organophosphorus poisoning (POP) scale, IQR[#], interquartile range. Mann–Whitney *U* test was applied for the comparison of central tendency between two groups

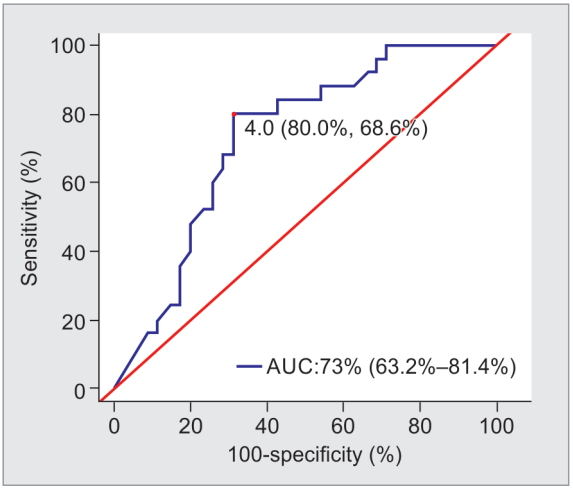

Fig. 2: Receiver operating characteristic curve for the use of the red blood cell cholinesterase (E-AChE) in units per gram of hemoglobin for predicting a moderate to severe poisoning as per the peradeniya organophosphorus poisoning severity scale

This curve shows that a cut-off of 4 IU/mL provided an area under the curve (AUC) of 73% (63.2–81.4%), with a sensitivity of 80% and specificity of 68.6%

where laboratory support for evaluating E-AChE or BChE levels may be lacking in most Government and Rural Health Centers, this handheld device offers a practical solution.

We found a significant association between admission E-AChE levels and moderate to severe toxicity, as determined by the POP severity score. Additionally, higher initial doses of atropine were required for patients with lower blood E-AChE levels. In contrast,

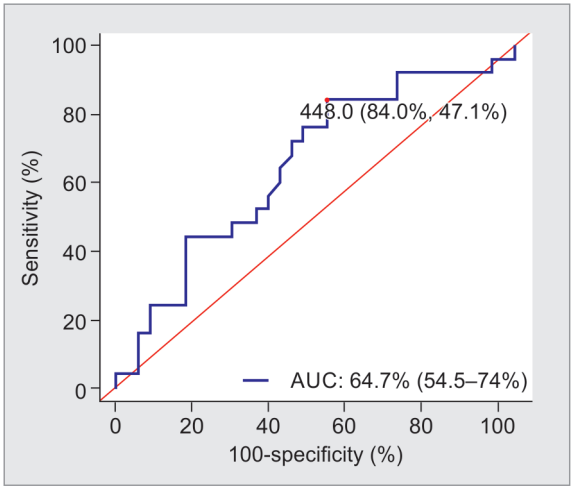

Fig. 3: Receiver operating characteristic curve for the use of plasma pseudocholinesterase (BChE) in units per liter for predicting moderate to severe poisoning as per the peradeniya organophosphorus poisoning (POP) severity scale[25–27]

The curve shows that a cut-off of 448.0 U/liter provided an AUC of 64.7% (54.5–74.0%), with a sensitivity of 84.0% and specificity of 47.1%. However, this AUC was significantly lower than the AUC obtained from the analysis of whole-blood E-AChE

admission plasma BChE levels lacked correlations in predicting severity, atropine requirements, and intermediate syndrome. This reveals the need to move from BChE-based screening to E-AChE-based protocol for OP and carbamate poisonings. More than half of our patients needed mechanical ventilation and ICU admission which may be due to referral bias. A tracheostomy was needed for prolonged ventilation, mainly due to intermediate syndrome or ventilator-associated pneumonia. We diagnosed intermediate syndrome in 30% of cases, emphasizing its significant occurrence in cases of OP poisoning. These varying requirements of atropine doses, the requirement for mechanical intubation and ICU admissions in different severity of poisoning as per the POP scale, underscores the importance of tailoring treatment plans based on the severity of OP poisoning, providing valuable insights for optimizing treatment strategies and patient management.

About one-third of individuals exhibited delirium, necessitating the use of restraints. The relatively high incidence of these symptoms raises concerns about the potential overuse of atropine and prompts further investigation into determining the optimal method of atropinization and when to stop atropine infusion. However, no severe toxicity related to atropine was observed in our patients, and the delirium resolved upon adjusting the infusion rate or discontinuing the drug. These findings highlight the importance of closely monitoring and adjusting atropine administration to minimize adverse effects while ensuring effective treatment. There were a total of three (5%) deaths during hospitalisation indicating a comparatively lower mortality rate for OP and carbamate poisoning than previously reported in the literature.[29,30] This positive outcome can be attributed to the presence of a well-equipped ICU and the provision of high-quality care within our healthcare setting.

Limitations of the Study

While our study provides valuable insights into the correlation between admission E-AChE, severity, and outcomes in OP and carbamate poisoning, certain limitations should be acknowledged. Our sample size was restricted to 60 patients, which may not fully represent the population admitted to our ER, and this may be due to our exclusion criteria. Additionally, missed opportunities for collecting admission samples of E-AChE occurred in some instances.

Implications for Future Research and Recommendation

The ChE check mobile device, used for estimating E-AChE, provided rapid results and demonstrated satisfactory performance in our study. However, future larger studies are needed to validate and replicate these findings. This may help in cementing its status as a reliable technique to confirm and prognosticate OP poisonings.

Conclusion

The utilization of the handheld check ChE mobile device can be a valuable tool for rapid prognostication of patients with OP and carbamate poisoning, facilitating the early referral of potentially critically ill patients. Our study revealed a moderate negative correlation between E-AChE levels and the atropine requirements. Low E-AChE levels were also associated with an increased likelihood of complications, including the need for ventilation and ICU admission. Furthermore, our findings indicate that admission pseudo cholinesterase levels do not correlate with disease severity, atropine requirements, and ICU admission. Additionally, we observed a strong correlation between the POP severity score and the need for ICU admission, ventilation, and atropine requirements. Therefore, integrating the POP severity score into the assessment of patients presenting to the ER of a Tertiary Care Center can aid in determining the severity of the disease.

Ethical Approval

The authors of this publication declare that this scientific work follows the EQUATOR Network's reporting quality, formatting, and reproducibility requirements. The authors further state that this clinical study was initiated after approval from the Institutional Evaluation Board/Ethics Committee review and that the protocol/approval number is [IRB Minute No. 10020: dated April 4, 2016]. We also certify that the contents of this submission have not been plagiarized and that we have conducted a Plagiarism Check.

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