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Predicting Outcome in Organophosphorus Poisoning Using RBC Cholinesterase and Serum Cholinesterase Values: A Hospital-based Longitudinal Study

Saswati Kar[1] Nihar Ranjan Mohanty[1] Bhagyashree Panda[1] Roma Rattan[2] Anurag Choudhury[3] Suchismita Panda[4] Pramod Kumar Rout[5] Bhaktabandhu Das[6] Biswaranjan Prusty[5] Pravat Kumar Thatoi[5]

[1] Department of Medicine, S.C.B. Medical College, Cuttack, Odisha, India
[2] Department of Biochemistry, Government Medical College, Sundergarh, Odisha, India
[3] NTPC Hospital, TSTPS, Kaniha, Odisha, India
[4] Department of Biochemistry, Dharanidhar Medical College, Keonjhar, Odisha, India
[5] Department of Medicine, Dharanidhar Medical College, Keonjhar, Odisha, India
[6] Department of Psychiatry, Dharanidhar Medical College, Keonjhar, Odisha, India

Address for correspondence Dr. Pravat Kumar Thatoi, MD, Department of Medicine, Dharanidhar Medical College, Keonjhar 758002, Odisha, India (e-mail: drpravatthatoi@yahoo.co.in).

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Abstract

Background Organophosphorus (OP) poisoning is a leading cause of mortality due to self-harm in Asian countries, including India. Red blood cell cholinesterase (RBC-ChE) and serum cholinesterase (serum-ChE) levels are used for predicting outcomes. There is a paucity of literature studying the RBC-ChE levels in OP poisoning and comparing it with the serum-ChE levels.

Methods This is a longitudinal study assessing the outcome in OP poisoning patients using the RBC-ChE and serum-ChE levels. Both enzyme levels are compared and correlated for adult patients presenting within 24 hours of consumption of the OP compound. Sensitivity and specificity are measured.

Results Of the 99 OP poisoning patients included, 20 patients did not survive, and 23 patients required ventilatory support. At admission, RBC-ChE (median, interquartile range [IQR]) was significantly different between survivors (45.2 [30.5–60] U/g Hb) and nonsurvivors (6.3 [4.2–13.4] U/g Hb), while serum-ChE (median, IQR) was not statistically different ($p = 0.061$) between survivors (350 [247–670]) and nonsurvivors (290 [182–415.8]). Similarly, RBC-ChE was significantly different between patients requiring a ventilator and those not requiring a ventilator (6.8 vs. 44.2 U/g Hb), whereas the serum-ChE values measured on admission were not significantly different for

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patients requiring a ventilator versus those not requiring a ventilator (290 vs. 348 U/L; $p = 0.119$). At the cutoff of 20 U/g Hb, RBC-ChE had 90.5% sensitivity and 91% specificity in predicting mortality. Kaplan–Meier survival showed the probability of survival decreased to nearly 50% if the time to reach the hospital was $\geq$4 hours.

Conclusion RBC-ChE was superior in predicting outcomes in OP poisoning patients compared with serum-ChE measured on the day of admission.

Introduction

Pesticide poisoning is a leading cause of mortality due to self-harm in lower- and middle-income countries.[1] The World Health Organization (WHO) estimates around 250,000 deaths occur due to poisoning each year globally and pesticides cause nearly 150,000 deaths.[2] These pesticides mostly comprise organophosphorus (OP) compounds like chlorpyriphos, profenofos, monocrotophos, phorate, dichlorvos, and methyl parathion, which belong to WHO toxicity classes Ia, Ib, and II.[3,4] Despite regulations, highly hazardous pesticides (HHPs) belonging to WHO class II like chlorpyriphos and profenofos, which have case fatality rates (CFRs) of 7.6 and 11%, respectively, are available in India.[5]

OP compounds irreversibly inhibit the enzyme acetylcholinesterase (AchE) by phosphorylating the serine hydroxyl group present in its active site.[6] Inhibition of the enzyme leads to excessive accumulation of acetylcholine, which causes overstimulation of muscarinic and nicotinic receptors, giving rise to the characteristic toxidrome.[7] Respiratory failure can be due to bronchospasm, bronchorrhea (both reversible with antimuscarinic agents such as atropine), or diaphragmatic paralysis that results from dysfunction at the level of neuromuscular junctions or central nervous system (CNS).[8] Scoring systems like Peradeniya OP Poisoning (POP) scale have been devised to assess severity at presentation based on clinical signs and to determine prognosis.[9]

Confirmation of the diagnosis is through estimation of the serum cholinesterase (serum-ChE) or butyrylcholinesterase activity, which is available readily.[10] Since the clinical manifestations of poisoning are due to the inhibition of acetylcholinesterase present in synapses, the estimation of butyrylcholinesterase (pseudocholinesterase) present in plasma does not give information on the severity of poisoning.[8] Serum-ChE is produced by the liver, and it can be affected by conditions like malnutrition, chronic liver disease, chronic kidney disease, chronic infection, and malignancy.[11] Red blood cell cholinesterase (RBC-ChE), on the other hand, based on structural and kinetic data, is similar to the acetylcholinesterase found in neuromuscular junction; therefore, estimation of RBC-ChE correlates with prognosis and outcome, especially for predicting respiratory failure.[12] A very low RBC-ChE activity (<10% of normal) is found to be associated with impaired neuromuscular transmission and RBC-ChE activities above 30% with normal muscle function.[13] In a study, OP poisoning patients with RBC-ChE activity of >30% did not require atropine vis-à-vis those with less than 10% activity who needed high doses of atropine.[14]

In the present study, we aim to correlate the RBC-ChE and serum-ChE values with the survival of patients with OP poisoning. This will help in triaging cases and efficient resource management.

Materials and Methods

Study Setting

This is a longitudinal study conducted in a tertiary care hospital catering to a large population of Eastern India. The study period was from December 2020 to July 2021.

Participants

All adult patients presenting within 24 hours of consumption of OP compound were included in the study. Patients with known medical illnesses like malnutrition, chronic liver disease, chronic kidney disease, chronic infection, chronic obstructive pulmonary disease, myopathy, and malignancy or those who had consumed other drugs or toxins along with OP compound were excluded. All patients presenting to the hospital during the study period and fitting our inclusion criteria were considered in the study and hence no formal sample size was calculated.

Methodology

After obtaining written informed consent from the participants, information regarding the name of the OP compound consumed, time of consumption, treatment at the primary care hospital, and history of any comorbidities was obtained. All patients were subjected to a thorough clinical examination, and the POP scale[9] was applied for grading the severity as mild, moderate, and severe. All patients were treated as per hospital protocol with gastric lavage and administration of atropine and pralidoxime. Atropine was given in the form of bolus doses of 1.2 to 3 mg intravenous (IV), doubling doses every 5 minutes till end points of atropinization were achieved and subsequently maintained on a dose of 10% of the initial dose per hour, which ranged from 2 to 8 mg/h. This was slowly tapered, usually in 48 to 72 hours depending on clinical evaluation. As per the WHO recommendation, injection PAM was given at a dose of 2 g IV stat (30 mg/kg body weight) followed by 1 to 2 g IV 6 hourly (10 mg/kg body weight) for 48 to 72 hours.[15] In all study participants, approximately 5-mL blood was collected at the time of admission (day 1) for RBC-ChE, serum-ChE, serum electrolytes, liver function test, renal function test, and complete blood

count. Serum-ChE estimation was repeated on days 2 and 3. Whole blood collected for estimation of RBC-ChE was rapidly diluted with phosphate buffer saline and cooled so as to inhibit the reactions between OP, oximes, and RBC-ChE. Clinical severity was assessed and categorized according to the POP scale. A score of 0 to 3 is considered mild, 4 to 7 moderate, and 8 to 11 severe. Patients were subsequently followed up till discharge from the hospital or death. Atropine doses and duration, oxime doses and duration, complications, need for mechanical ventilation, and duration of mechanical ventilation were documented. Serum-ChE estimation (normal range as per laboratory: 4,000–11,000 U/L) was done using Agappe DGKC (Deutsche Gesellschaft Fur Klinische Chemie /German Society of Clinical Chemistry) colorimetric method. RBC-ChE estimation was done utilizing the modified Ellman method. According to a study by Sanz et al,[16] normal RBC-ChE values in a group of subjects unexposed to OP were 39.30 ± 5.05 U/g Hb for men and 42.57 ± 6.85 U/g Hb for women. These values are used as a reference in our study.

Statistical Analysis

Data were analyzed using SPSS v21. Results of descriptive statistics were expressed as mean ± standard deviation (SD) for normally distributed data or median (interquartile range [IQR]) for skewed data for continuous variables and frequency (percentage) for categorical variables. Parametric tests like Student's *t*-test and Pearson's chi-squared test were used for normally distributed continuous and categorical variables, respectively. Nonparametric tests like the Mann–Whitney *U* test for continuous variables of two independent samples were used. The RBC-ChE and serum-ChE levels measured on days 1, 2, and 3 were correlated with other continuous variables using Spearman rank's correlation (skewed data), and correlation coefficient Spearman's rho was noted. Kaplan–Meier (KM) survival analysis was done for the outcome of the study and the time-to-event survival graph was plotted. Asymptotic two-tailed *p*-value of less than 0.05 was considered statistically significant and a *p*-value of less than 0.001 was considered highly significant.

Results

A total of 99 OP poisoning patients were included in the study, with age ranging from 18 to 80 years and the majority belonging to the age group of 21 to 30 years. Of these patients, 48 were males and 51 were females. The major OP compounds consumed were chlorpyrifos ($n = 64$), followed by profenofos ($n = 8$), phorate ($n = 12$), monocrotophos ($n = 7$), and a few other compounds like ethephon ($n = 3$), dimethoate ($n = 2$), acephate ($n = 1$), dichlorvos ($n = 1$), and thimet ($n = 1$). Most patients (53.5%) reached the hospital within 4 hours, of which 43.4% presented within 2 hours of poisoning. The mean time to reach the hospital was 2.3 hours (SD = 1.06). The K-M survival curve demonstrated that mortality increased and greater atropine dosages were needed when therapy was delayed by more than 4 hours. Clinical features presented were salivation and frothing (84.8%), lacrimation (32.3%), diaphoresis (20.3%), urination (15.3%), defecation (18.2%), vomiting (67.7%), breathlessness (34.3%), and altered sensorium (60.6%). Our study categorized 32 patients as mild, 50 as moderate, and 17 as severe using the POP scale. Cholinergic crisis (reappearance of cholinergic symptoms and signs during the course of treatment with atropine) was observed in 12 cases. Intermediate syndrome (tachypnea, absence of neck lift, falling oxygen saturation, and hypoxic encephalopathy indicating respiratory muscle paralysis) developed in 14 patients. A total of 23 patients were mechanically ventilated. In our study, 15/23 (65.23%) ventilated patients succumbed and 5 cases succumbed to intermediate syndrome before mechanical ventilation could be provided, making the total number of deceased to be 20.

►**Table 1** compares the descriptive statistics of various parameters among patients who survived and who did not. The median age of the patients who survived the event was 28 years (range: 21–40 years) and that of the patients who did not survive was 55 years (range: 36–60 years). The median time to reach the hospital was longer in the deceased group compared with survivors (3 vs. 2 hours) with a *p*-value of 0.008. Similarly, RBC-ChE on day 1 and serum-ChE measured on days 1, 2, and 3 for the survivor and deceased groups were 45.2 vs. 6.3 U/g Hb ($p < 0.001$) and 350 versus 290 U/L ($p < 0.061$), 454 versus 198 U/L ($p < 0.001$), and 480 versus 148.5 U/L ($p < 0.001$), respectively. Among the deceased group, 19 patients (95%) had complications and 15 patients (75%) required ventilator support.

►**Table 2** compares the median RBC-ChE on day 1 and serum-ChE values measured on days 1, 2, and 3 among those on ventilators and those who were not. The median RBC-ChE on day 1 and serum-ChE values measured on days 1, 2, and 3 were 6.8 versus 44.2 U/g Hb ($p < 0.001$) and 290 versus 348 U/L ($p = 0.119$), 210.5 versus 444 U/L ($p < 0.001$), and 148.5 versus 453 U/L ($p < 0.001$) among the patients requiring a ventilator versus not requiring a ventilator, respectively.

►**Table 3** demonstrates the correlation of different parameters with RBC-ChE and serum-ChE values measured on days 1, 2, and 3. The correlation coefficient, Spearman's rho for RBC-ChE and serum-ChE values, measured on days 1, 2, and 3 against time taken to reach the hospital were –0.254 ($p = 0.011$) and –0.094 ($p = 0.355$), –0.252 ($p = 0.012$), and –0.299 ($p = 0.003$), respectively. Similarly, Spearman's rho for RBC-ChE and serum-ChE values measured on days 1, 2, and 3 against POP scores were –0.13 ($p = 0.2$) and –0.159 ($p = 0.117$), –0.29 ($p = 0.004$), and –0.252 ($p = 0.012$), respectively.

►**Fig. 1** depicts the receiver operating characteristic (ROC) curve with RBC-ChE, serum-ChE-D1, serum-ChE-D2, and serum-ChE-D3 evaluated for outcome. At a cutoff value of 20, RBC-ChE has an area under the curve (AUC) of 0.906 (0.831–0.981), sensitivity of 90.5%, and specificity of 91% in predicting mortality. RBC-ChE is clearly a better indicator of mortality than serum-ChE (AUC for D1, D2, and D3 are 0.652, 0.837, and 0.883, respectively). RBC-ChE is a better predictor compared with serum-ChE-D1.

Table 1 Descriptive statistics of various parameters among the survivors and deceased among OP poisoning patients ($N = 99$)

Parameters	Survivors ($n = 79$), median (IQR)/n (%)	Nonsurvivors ($n = 20$), median (IQR)/n (%)	p-value
Age (y)	28 (21–40)	55.5 (36–60)	<0.001
Sex, male/female	36 (45.6)/43 (54.4)	12 (60)/8 (40)	0.319
Time taken to reach the hospital (h)	2 (2–3)	3 (2–4)	0.008
RBC-ChE (U/g Hb)	45.2 (30.5–60)	6.3 (4.2–13.4)	<0.001
>40	52 (65.8)	1 (5)	
25–40	18 (22.8)	0 (0)	
5–25	5 (6.3)	13 (65)	
<5	4 (5.1)	6 (30)	
Serum-ChE on day 1 (U/L)	350 (247–670)	290 (182–415.8)	0.061
>500	29 (36.7)	1 (5)	
250–500	28 (35.4)	10 (50)	
100–250	17 (21.5)	7 (35)	
<100	5 (6.3)	2 (10)	
Serum-ChE on day 2 (U/L)	454 (261–843)	198 (140.5–266)	<0.001
>500	36 (45.6)	1 (5)	
250–500	26 (32.9)	4 (20)	
100–250	16 (20.3)	13 (65)	
<100	1 (1.3)	2 (10)	
Serum-ChE on day 3 (U/L)	480 (268–965)	148.5 (112.8–251)	<0.001
>500	37 (46.8)	0 (0)	
250–500	26 (32.9)	5 (25)	
100–250	15 (19)	13 (65)	
<100	1 (1.3)	2 (10)	
POP score	4 (2–4)	8 (6–8)	<0.001
Mild (0–3)	29 (36.7)	3 (15)	
Moderate (4–7)	44 (55.7)	6 (30)	
Severe (8–11)	6 (7.6)	11 (55)	
Atropine dose (mg), mean ± SD	183.5 ± 68.74	225 ± 110.62	0.008
Complications, present/absent	12 (15.2)/67 (84.8)	19 (95)/01 (05)	<0.001
Ventilator, required/not required	8 (10.1)/71 (89.8)	15 (75)/05 (25)	<0.001

Abbreviations: ChE, cholinesterase; IQR, interquartile range; POP, Peradeniya Organophosphorus Poisoning; RBC, red blood cell.

Table 2 Comparison of RBC-ChE, serum-ChE on days 1, 2, and 3 with regard to ventilatory support ($N = 99$)

Parameters	Mechanical ventilation (MV), median (IQR)		p-value
	On MV ($n = 23$)	Without MV ($n = 76$)	
RBC-ChE	6.8 (4.2–13.4)	44.2 (29.4–59)	<0.001
Serum-ChE on day 1	290 (159.5–427.8)	348 (244–643)	0.119
Serum-ChE on day 2	210.5 (169.5–266)	444 (253–809)	<0.001
Serum-ChE on day 3	148.5 (114.8–231.5)	453 (267–946)	<0.001

Abbreviations: ChE, cholinesterase; IQR, interquartile range; RBC, red blood cell.

Table 3 Spearman's rank correlation of different parameters with RBC-ChE, serum-ChE on days 1, 2, and 3 ($N = 99$)

Parameters (Spearman's rho)	RBC-ChE	Serum-ChE on day 1	Serum-ChE on day 2	Serum-ChE on day 3
Time to reach hospital				
Correlation coefficient	−0.254*	−0.094	−0.252*	−0.299*
p-value	0.011	0.355	0.012	0.003
POP score				
Correlation coefficient	−0.13	−0.159	−0.29*	−0.252*
p-value	0.2	0.117	0.004	0.012
Atropine dose				
Correlation coefficient	0.041	−0.181	−0.244*	−0.253*
p-value	0.684	0.073	0.015	0.011
Hospital stay				
Correlation coefficient	−0.045	−0.233*	−0.188	−0.174
p-value	0.656	0.02	0.062	0.085

Abbreviations: ChE, cholinesterase; POP, Peradeniya Organophosphorus Poisoning; RBC, red blood cell.
*states that corresponding correlation coefficient value is statistically significant, i.e, p-value is less than 0.05.

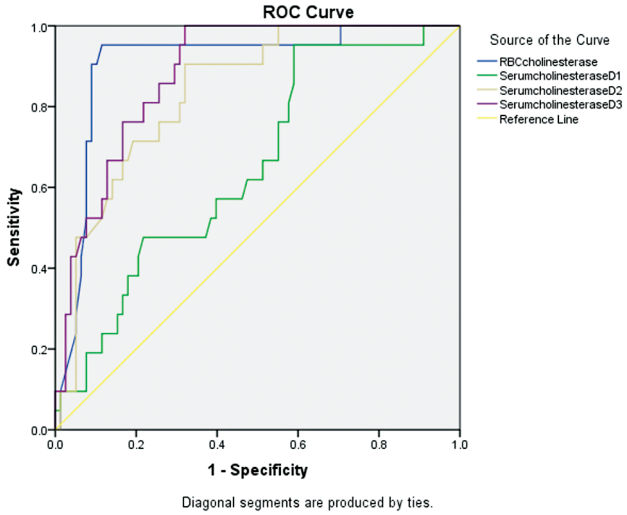

Fig. 1 ROC curve to demonstrate sensitivity and specificity of RBC-ChE on day 1 and serum-ChE on days 1, 2, and 3 for predicting outcome. ChE, cholinesterase; RBC, red blood cell; ROC, receiver operating characteristic.

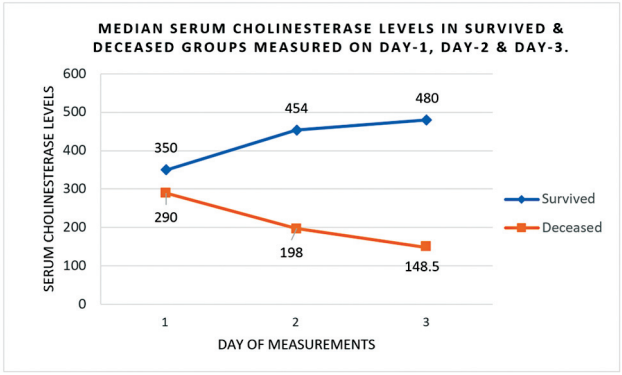

Fig. 2 Line chart comparing median values of serum-ChE on days 1, 2, and 3 among the survivors and deceased patients ($N = 99$).

►**Fig. 2** depicts a line chart showing the median values of serum-ChE values measured on days 1, 2, and 3 among the survivors and deceased group. There is a gradual decrease in the values of serum-ChE on days 1, 2, and 3 (290, 198, and 148.5 U/L) among the deceased group and gradual increase in the serum-ChE levels (350, 454, and 480 U/L) among the survivors.

►**Fig. 3** demonstrates the KM survival plot. According to the survival analysis, the probability of survival following ingestion of organophosphate poison decreases to approximately 50%, if the time to reach the hospital is ≥4 hours.

Discussion

OP poisoning is an important public health problem with a high mortality rate when appropriate treatment is not provided timely. These compounds are easily available in rural agricultural communities and thus the highest incidence rate is seen in India.

In the present study, patients were distributed almost equally across gender. The mean age of the patients was 36.7 years, which is comparable with other studies such as by Nouira et al and Patel et al.[17,18] One-third of cases belonged to the age group of 21 to 30 years (31.3%) similar to previous studies. Chlorpyriphos, a diethyl OP compound, was our study's most widely consumed compound.

We used the POP score to objectify and grade the clinical signs to analyze with cholinesterase values and find a correlation. It uses pupil size, heart rate, respiratory rate, level of consciousness, presence of fasciculation, and seizures as parameters. The POP scale has been used in previous studies like Rehiman et al,[19] which found a good correlation between the POP scores and the need for mechanical ventilation and total dose of atropine. In our study, the median POP scores among ventilated and nonventilated patients were 6 and 3, respectively, the difference being statistically significant. A negative correlation was found between the

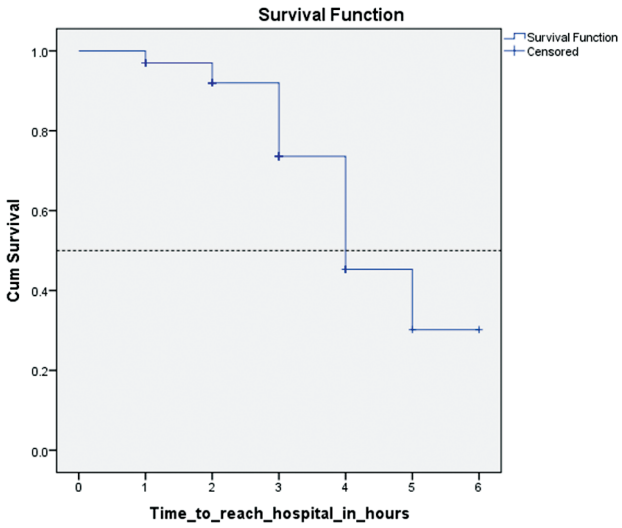

Fig. 3 Kaplan–Meier time-to-event survival plot.

POP score and the serum-ChE values on days 2 and 3, with a significant difference between those who survived and those who did not (median score: 4 vs. 8). We found that a higher dose of atropine was required in patients presenting late, having lower POP scores, and requiring mechanical ventilation. It also has a significant correlation with serum-ChE values on days 2 and 3. The RBC-ChE value had no significant correlation with the POP score.

The overall mortality following OP poisoning varies between 4 and 30%.[20] In the present analysis, the overall mortality was 20.2% ($n = 20$) and mortality in those who required mechanical ventilation was 65.23%. The mortality rate in mechanically ventilated patients was reported to be 50% in Sungur et al,[21] 22% in Patil et al,[22] and 8% in Hussain and Sultan.[23] Higher mortality in our study can be attributed to delays in intubation and the provision of mechanical ventilation due to the scarcity of intensive care unit (ICU) beds. The compounds that contributed to deaths were profenofos (CFR = 62.5%), chlorpyriphos (CFR = 19.04%), and phorate (CFR = 27.27%); profenofos was apparently the deadliest compound in our study. The patients who were mechanically ventilated were of older age group (mean = 48.75 years), had median (IQR) RBC-ChE of 6.8 U/g Hb (4.2–13.4), and serum-ChE on day 1 of 290 U/L (159.5–427.8). On analysis, it was noticed that the RBC-ChE value correlated better with the need for mechanical ventilation and the serum-ChE value on day 1 had no correlation; however, the serum-ChE values on days 2 and 3 had a correlation. This corroborates with findings in Nouira et al,[17] Rehiman et al,[19] and Aygun et al[24] that the serum-ChE level on the day of presentation has no role in predicting outcome. It was also observed that the serial serum-ChE level estimation had a role in predicting mortality as comparable with studies by Chen et al[25] and Yun et al in China,[26] which state that the absence of an increase in cholinesterase activity during the course of illness is associated with a poor outcome and serial measurements of cholinesterase gives a better guide to the treating physician.

Limitations and Recommendations

We could further extend the study by estimating the RBC-ChE values on successive days or on the day of ventilator requirement and find any significant correlation. A formal sample size calculation was not done in our study. Hence, more studies with larger sample sizes are recommended for validating the use of RBC-ChE in OP poisoning, studying among patients with comorbidities, and correlating the parameters during ventilatory support.

Conclusion

Estimation of the RBC-ChE activity in blood is the most accurate prognostic indicator for outcomes in OP poisoning patients. This is very important for triaging patients and managing complications promptly. Serial serum-ChE estimation also significantly portends the outcome. The POP scale is an important tool for determining severity in patients.

Compliance with Ethical Standards

The study was conducted in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Ethical Approval

The study was approved by the Institutional Ethics Committee of S.C.B. Medical College and Hospital, Cuttack, vide IEC/IRB no. 402/14.10.2020.

Informed Consent

Informed consent was obtained from each participant in written form in the local Odia language. In a situation where the participant could not provide consent, informed consent was obtained from their first-degree relative/legal guardian.

Author Contributions

S.K. contributed to the conception, data collection, and drafting of the manuscript. N.R.M. contributed to the study design and review of literature. B.P. contributed to review of the literature and revising the manuscript. R. R. contributed to biochemical measurements and review of the manuscript. A.C. contributed to statistical analysis, interpretation of data, and preparation of tables and figures. S.P. contributed to review of the manuscript. P. K.R. was responsible for reference management. B.D. provided assistance during patient interaction and contributed to review of the manuscript. B.R.P. contributed to review of the manuscript and the references. P.K.T. contributed to conception, interpretation of data, and review of the manuscript.

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Conflict of Interest

None declared.

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