Research Article

Prediction of Pralidoxime Dose in Patients with Organophosphate Poisoning Using Machine Learning Techniques

Babak Mostafazadeh [1], Shahin Shadnia [1], Sayed Masoud Hosseini [1], Mitra Rahimi [1], Haleh Talaie [2], Seyed Ali Mohtarami [3, *], Peyman Erfan Talab Evini [1], Joshua King [4]

[1] Department of Clinical Toxicology, Toxicological Research Center, Excellence Center of Clinical Toxicology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Toxicological Research Center, Loghman-Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Department of Forensic Medicine, Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran
[4] Maryland Poison Center, University of Maryland Medical Center, Baltimore, USA

*Corresponding author: Department of Forensic Medicine, Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran. Email: mohtarami.seyedali@gmail.com

Abstract

Background: Early and appropriate antidotal therapy is crucial for patients with organophosphate poisoning.

Objectives: Given the lack of a comprehensive consensus on the optimal dose of pralidoxime for patients with organophosphate poisoning, this study aims to develop a machine learning-based prediction model to determine the individualized pralidoxime dose for these patients.

Methods: The dataset was divided into training and test sets with a 70:30 ratio. Feature selection was conducted using Pearson's correlation coefficient (filter approach) method. Both classification and regression were employed to develop the prediction model using the selected features. The performance of the developed models was evaluated using ten-fold cross-validation and various metrics, including sensitivity, specificity, accuracy, F1-score, and AUC. The models were implemented and assessed using the scikit-learn library in Python.

Results: After applying exclusion criteria, data from 325 patients were utilized to train and test the machine-learning models. In the classification approach, the random forest method achieved superior performance with an AUC of 98.6. In the regression approach, the gradient boosting regressor, with an R^2 value of 65.4, outperformed other algorithms. Feature selection revealed that muscular weakness, plasma cholinesterase activity, and blood urea nitrogen were the most significant predictors of pralidoxime dose in the classification model. In the regression model, the top predictors were age, HCO_3-VBG, and atropine bolus. Many of the selected features coincide with those identified in previous studies, with muscular weakness being particularly significant in both models.

Conclusions: The most effective algorithms could be employed to develop a clinical decision support system for personalized pralidoxime dosage prediction in patients with organophosphorus poisoning. However, the study is constrained by its small sample size, retrospective design, and the absence of an external validation cohort. Conducting a prospective multicenter study with a larger sample size is crucial to validate the findings of this study.

Keywords: Organophosphates, Pralidoxime Compounds, Machine Learning, Artificial Intelligence

1. Background

Organophosphate (OP) poisoning is a major global health issue caused by exposure to OP compounds, which are widely used as pesticides. Organophosphates are among the most common causes of accidental, occupational, and suicidal intoxications due to their widespread use, easy accessibility, and simplicity in synthesis (1). Despite the role of pesticides in enhancing agricultural productivity, concerns are increasing about their adverse effects on human health (2). Organophosphate poisoning is more prevalent in developing countries where highly hazardous pesticides (HHPs) are more readily available. Significant incidences of intentional or unintentional OP poisoning occur in the agricultural regions of developing countries in

South Asia and Southeast Asia, including China, India, Sri Lanka, Iran, and the Maldives (2, 3). Annually, the global death toll from OP poisoning is estimated to range from 250 000 to 350 000 (4). In rural areas, poisoning with organophosphorus compounds typically occurs deliberately with suicidal intent (5). One study reported that 51.7% of OP poisonings were deliberate, while 21.7% were accidental (4). Previous studies have indicated that intentional self-poisoning is associated with significantly higher mortality than unintentional poisoning (6). Given the high prevalence of intentional poisoning with organophosphorus compounds, particularly in developing countries, and the high mortality associated with it, implementing necessary therapeutic interventions for these patients is crucial.

Organophosphates inhibit the enzyme acetylcholinesterase (AChE) by phosphorylating the serine hydroxyl group on the enzyme. Acetylcholinesterase is responsible for hydrolyzing the neurotransmitter acetylcholine (ACh) at cholinergic synapses. Therefore, AChE inhibition leads to the accumulation of ACh at the cholinergic synapse, resulting in prolonged stimulation of nicotinic and muscarinic ACh receptors, which manifests as OP toxidrome (1, 7). In addition to supportive care, the standard treatment includes three main therapeutic approaches: Atropine to block muscarinic receptors, oxime-type reactivators (e.g., pralidoxime, obidoxime) to dephosphorylate the inhibited AChE and benzodiazepines for seizure management.

In Iran, pralidoxime chloride (2-PAM) is the oxime of choice and is commonly used as an antidote for OP poisoning. It works by reactivating AChE, thus reducing the accumulation of ACh (8). For adults, the initial recommended dose of pralidoxime chloride typically ranges from 1 to 2 grams, followed by a continuous infusion at a rate of 250 to 500 mg per hour. However, dosing guidelines can vary based on the specific product used and the severity of the poisoning. Close monitoring of the patient's clinical response is crucial to determine the need for additional doses or adjustments in the infusion rate. In pediatric patients, the dose of pralidoxime is generally calculated based on body weight, with an initial dose typically ranging from 20 to 50 mg/kg, followed by a continuous infusion at a rate of 5 to 10 mg/kg per hour (9-11).

There is a divergence of opinion regarding the effectiveness of pralidoxime in treating OP poisoning; some studies have reported that its administration leads to a decrease in mortality among patients poisoned with organophosphorus agents (12-15), while others

indicate no effect (16, 17). Several previous studies examining the effectiveness of various dosages of pralidoxime are outlined in Table 1 (11, 14, 16, 18-25). The appropriate dose of pralidoxime for a specific individual depends on several factors, including the severity of poisoning, age, weight, and individual response (26). Additionally, some studies recommend high-dose pralidoxime (12), while others have reported that high doses may be associated with a higher mortality rate and recommend low-dose pralidoxime (27). With the expansion of information technology in many research fields, including healthcare, real-world studies such as non-interventional and observational studies have become significant data sources for clinical research (28). Compared to traditional models, machine learning approaches offer immense benefits in handling real-world evidence. Unlike traditional models, which cannot handle complex, interacting, high-dimensional variables, machine learning models are more accurate and provide greater generalizations (29). The use of machine learning techniques based on real-world research has become popular recently, with examples including models for predicting tacrolimus blood concentration in patients with autoimmune diseases, the prediction of vancomycin dose through XGBoost, and the prediction of warfarin maintenance dose through LightGBM (30-32).

2. Objectives

In this study, we aimed to predict an optimal pralidoxime therapeutic dose based on real-world evidence, including initial symptoms, clinical presentation, vital signs, and laboratory parameters at presentation, using machine learning methods to enhance its efficacy in patients poisoned by OPs.

3. Methods

3.1. Study Population

The roadmap of the proposed system for predicting pralidoxime dose in patients with OP poisoning is illustrated in Figure 1. This retrospective study was conducted at Loghman Hakim Hospital, Tehran, Iran's primary referral center for poisoned patients, from March 2016 to April 2021. The study included patients aged 14 years and older who had been poisoned with OPs and met specific criteria. These criteria included documented OP exposure and a plasma cholinesterase (PChE) activity of less than 4300 U/L upon admission, indicative of acute OP poisoning (33). A total of 325 patients were included, particularly those who received

commonly recommended pralidoxime dose regimens. These regimens typically involved an initial intravenous infusion of 1 - 2 g (10 - 20 mg/mL) over 15 - 30 minutes, followed by a continuous infusion of 500 mg/h until 24 hours after the patient was weaned from atropine. The study aimed to predict the outcome of dried pulmonary secretions and adequate oxygenation following pralidoxime administration. Exclusion criteria included non-receipt of pralidoxime, multidrug toxicity, and the presence of severe chronic comorbidities. Ethical approval for the study was obtained from the ethics committee (IR.SBMU.RETECH.REC.1401.257), and informed consent was obtained from all participants.
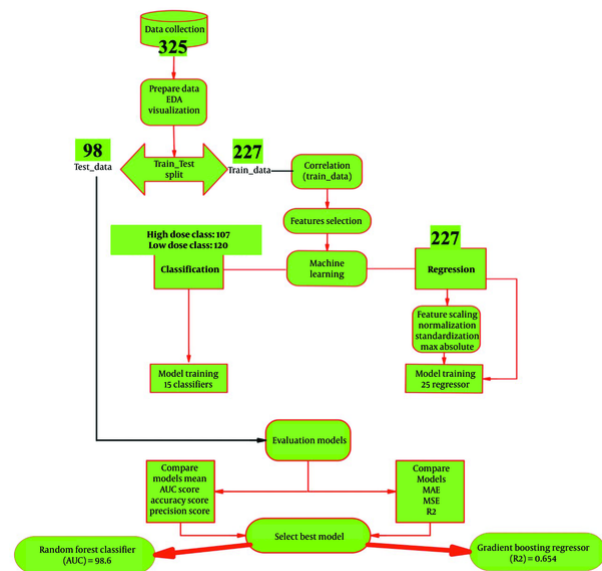

Figure 1. Graphical abstract: The roadmap of the proposed system to predict pralidoxime dose in patients with organophosphate poisoning

3.2. Collection and Processing of Data

Data for this study were obtained from electronic medical records. Two researchers reviewed the medical records of the patients, and a questionnaire was used to extract clinical information from the electronic databases of Loghman Hakim Hospital. The questionnaire covered various patient demographics, medical history, symptoms, and laboratory test results, as well as hospital-related factors such as the need for intubation and duration of hospitalization. The dataset underwent several preparation processes, including the removal of rows with missing values greater than 70%,

application of min-max scalar and standard scalar, data validation, under-sampling, and splitting of the dataset.

3.3. Feature Selection

Feature selection in machine learning involves identifying the most relevant attributes or parameters to improve model performance. In this research, the filter approach using Pearson's correlation coefficient was employed to select features by assessing the correlation between each variable and the predictive outcome. The aim was to identify the key predictors of the total pralidoxime dose necessary for maintaining sufficient oxygenation. Only variables demonstrating a strong correlation with the predictive outcome, such as dried pulmonary secretions and adequate oxygenation, were retained through the feature selection process. Variables with zero correlation coefficients were excluded from the feature subset, while those with high coefficients were included in the selected variables subset.

3.4. Statistical Analysis

Based on the outcomes of the Kolmogorov-Smirnov and Shapiro-Wilk tests, it was determined that all continuous variables exhibited non-normal distributions. Consequently, these variables were represented by their median values and interquartile ranges and were analyzed using the Kruskal-Wallis and Mann-Whitney U tests. Categorical variables were depicted in terms of absolute frequencies (n) and were analyzed using the chi-square test.

3.5. Model Development and Performance Evaluation

The prediction model for pralidoxime dose in patients poisoned by OPs was assessed using two methods: (1) Regression, with pralidoxime dose considered as a continuous variable; and (2) classification, with pralidoxime dose divided into two classes, low dose, and high dose. In the low dose class, patients received total doses of less than 14 000 g, and in the high dose class, patients received total doses of 14 000 g or more. For the first method, 25 machine learning models were used, and for the second method, 15 machine learning models were trained. Models with the best performance are listed in Table 2 (the top ten models for the regression method) and Table 3 (the top 14 models for the classification method). A ten-fold cross-validation technique was employed to train and test the machine learning algorithms using both complete and selected feature datasets. This method involves dividing the dataset into ten sections and

performing the holdout method ten times. The final dataset was randomly split into training (70%) and testing (30%) sets. Model creation, hyper-parameter tuning, and model performance evaluation were conducted using these datasets. This approach prevents random data bias and ensures an equal distribution of data between the training and test sets. It is important to note that the testing dataset was not used during the training process. Hyperparameters were tuned using the training dataset through the cross-validation method. Python software was used to develop a model utilizing classification models. The performance of the classification algorithms was assessed by testing them on the testing dataset after training. Five commonly used efficiency testing metrics, including sensitivity, specificity, accuracy, F1-score, and AUC, were utilized to evaluate the effectiveness of classification algorithms in predicting the pralidoxime dose in OP-poisoned patients. These performance measures were then used to compare the performance of each trained classifier with that of other machine-learning systems. The efficiency evaluation metrics for the classifiers are as follows:

$$Accuracy = \frac{TP + TN}{TP + YN + FP + FN} \times 100$$

$$Recall\ (aka\ sensitivity) = \frac{TP}{TP + FN} \times 100$$

$$Presicion = \frac{TP}{TP + FP} \times 100$$

$$f - measure = 2\frac{Presicion \times Recall}{Presicion + Recall}$$

Four performance measures were employed in the regression method to evaluate the performance of each algorithm: Mean absolute error (MAE), mean squared error (MSE), root mean squared error (RMSE), and R-squared (R^2). The calculations for these metrics are as follows:

$$MAE = \frac{1}{n} \sum_{j=1}^{n} |y_j - \hat{y}_j|$$

$$MSE = \frac{1}{n} \sum_{j=1}^{n} \left(y_j - \hat{y}_j\right)^2$$

$$RMSE = \sqrt{\frac{1}{n} \sum_{j=1}^{n} \left(y_j - \hat{y}_j\right)^2}$$

In the process of regression analysis, we employed the standardization technique to scale the variables. Standardization involves centering the values around the mean and adjusting them to have a unit standard deviation. This is achieved by dividing the variable by its standard deviation after subtracting the mean, as indicated by the following equation:

$$X_{Standard} = \frac{X - mean(X)}{Standard\ Deviation(X)}$$

4. Results

4.1. Patients

After a comprehensive review of electronic medical records, a total of 5,380 patients diagnosed with OP poisoning were identified within the database, forming the primary cohort. Among them, 983 patients had incomplete medical records, and 4,072 patients were excluded based on predetermined exclusion criteria. Specifically, 383 patients had a normal range of PChE, 1,057 patients had multidrug toxicity, 937 patients had chronic comorbidity, 529 patients were admitted more than 24 hours after poisoning, 549 patients were below 14 years of age, and 617 patients did not receive pralidoxime. Ultimately, 325 patients were enrolled in the study. Figure 2 depicts the patient selection process. The descriptive characteristics of the study sample are presented in Table 4.
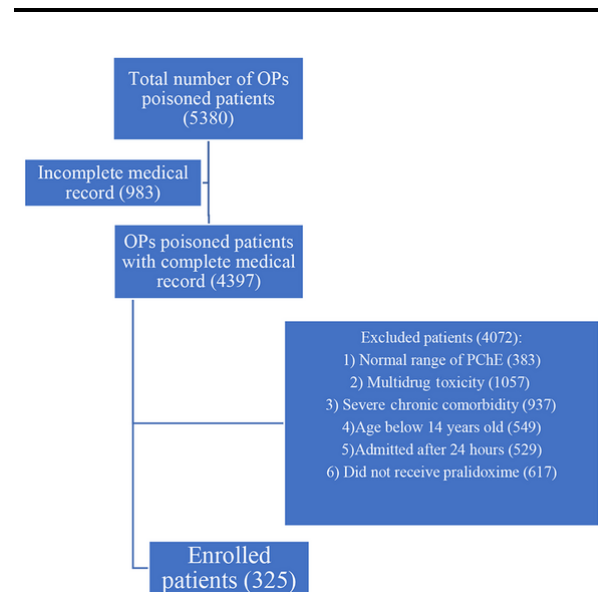

Figure 2. Patient selection flowchart

Table 2. Results of Ten-Fold Cross-Validation for Regressors Performance on Selected Predictors After Feature Scaling in Regression Method

Index	Model	MAE	MSE	RMSE	R^2	RMSLE	MAPE
Gbr	Gradient boosting regressor	9208.1856	265695067.5245	15210.5268	0.6540	0.7210	0.8991
light gum	Light gradient boosting machine	11082.3208	411516903.5829	18637.1318	0.5818	0.8653	1.2540
Et	Extra trees regressor	9964.7046	390583726.4613	17809.5835	0.4884	0.7287	0.9194
Ada	Adaboost regressor	14937.2844	428589688.6916	19027.8917	0.4837	1.1143	2.2290
xgboost	Extreme gradient boosting	9210.9117	342642130.7921	17211.7812	0.4199	0.7087	0.9305
Rf	Random forest regressor	11670.8163	433264351.1262	19619.4416	0.4145	0.7812	1.0514
Huber	Huber regressor	16389.3648	1018552916.3411	27720.5679	0.1742	1.1506	1.2774
Par	Passive aggressive regressor	16079.8772	1110867086.3911	29187.1724	0.0923	1.1319	1.0646
En	Elastic net	19619.8389	1026946561.5622	29350.4610	0.0035	1.2072	2.2364
Dt	Decision tree regressor	10381.8142	832112670.2866	24221.9796	0.0017	0.8261	0.7595

Table 3. Results of Ten-Fold Cross-Validation for Classifiers Performance on Selected Predictors in Classification Method

Index	Model	Accuracy	AUC	Recall	Precision	F1	Kappa
rf	Random forest classifier	0.9152	0.9865	0.9061	0.9308	0.9169	0.8307
light gum	Light gradient boosting machine	0.9073	0.9756	0.9159	0.9129	0.9107	0.8145
gbc	Gradient boosting classifier	0.9071	0.9584	0.9318	0.896	0.9125	0.8136
ada	Ada boost classifier	0.8897	0.9218	0.897	0.8968	0.8945	0.7786
et	Extra trees classifier	0.8798	0.9619	0.872	0.9013	0.883	0.7599
xgboost	Extreme gradient boosting	0.8763	0.9548	0.8826	0.881	0.879	0.7528
lda	Linear discriminant analysis	0.8275	0.8515	0.8379	0.8314	0.8328	0.6544
ridge	Ridge classifier	0.7966	0.0	0.8212	0.7942	0.8044	0.5924
dt	Decision tree classifier	0.7832	0.7839	0.7879	0.7967	0.7829	0.5672
lr	Logistic regression	0.748	0.8254	0.7871	0.751	0.7651	0.4947
qda	Quadratic discriminant analysis	0.7069	0.8036	0.6477	0.826	0.6635	0.4168
knn	K neighbors classifier	0.6947	0.7909	0.7015	0.7225	0.7043	0.3898
nb	Naive bayes	0.6856	0.7843	0.7682	0.6856	0.7195	0.363
Svm	SVM - linear kernel	0.5796	0.0	0.5705	0.6766	0.5375	0.1577

4.2. Feature Selection

Significant and relevant features for predicting the pralidoxime dose in OP-poisoned patients were selected using Pearson's correlation coefficient (filter approach). Figure 3 shows the top ten variables selected for the classification method, where muscular weakness, PChE activity, and blood urea nitrogen (BUN) scored the highest for predicting pralidoxime dose. In the regression method, after scaling the variables using the standardization technique, the top ten features in predicting the dose of pralidoxime from most to least important were age, HCO_3-VBG, bolus of atropine, aspartate aminotransferase (AST), pulmonary rale, PH-VBG, PChE activity, muscular weakness, BUN, and alanine transaminase (ALT) (Figure 4).
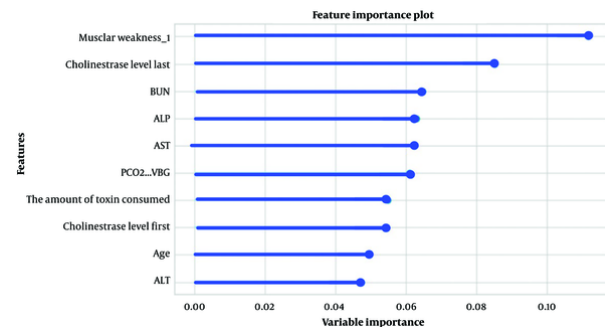
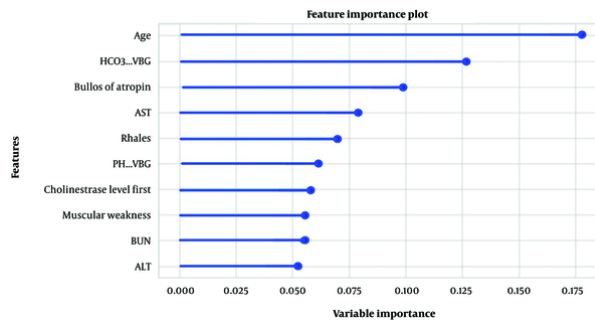**Figure 3.** Variables are selected by feature selection in the classification method.

Figure 4. Variables are selected by feature selection using the regression method.

Figure 5. The learning curve of the regression method before (A) and after (B) feature scaling
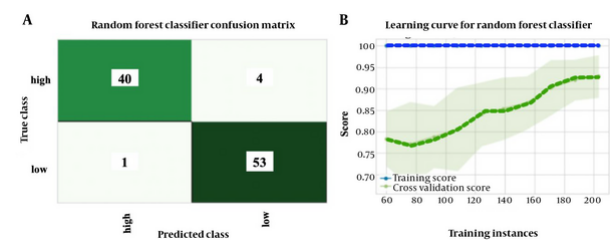
Figure 6. The confusion matrix (A) and learning curve (B) for the classification method

4.3. Performance of Prediction Models

Performance metrics were calculated to compare the effectiveness of prediction models in classification and regression methods. Table 2 presents the results of the top ten prediction algorithms for the regression method using selected standard features to predict the pralidoxime dose in patients with OP poisoning. The gradient-boosting regressor emerged as the most accurate and responsive model, exhibiting the highest R^2 value. This prediction model had an MAE of 9208.19, an MSE of 265695067.52, an RMSE of 15210.52, and an R^2 of 65.4. Figure 5 depicts the learning curves of the regression method before (A) and after (B) feature scaling, demonstrating improved convergence of training and cross-validation scores after scaling. Table 3 summarizes the results of the top 14 prediction algorithms for the classification method using selected features to predict the pralidoxime dose in OP-poisoned patients. Based on ten-fold cross-validation findings, the random forest classifier showed the highest accuracy and sensitivity, as well as the highest AUC value among the classifiers tested. This model achieved a mean accuracy of 91.5%, a recall or sensitivity of 90.6%, a precision of 93.1%, an F1-score of 91.7%, Kappa statistics of 83.1%, and an AUC of 98.6. Figure 6 presents the confusion matrix (A) and learning curve (B) for this model, indicating a good fit as the training and cross-validation curves converge at a high score.
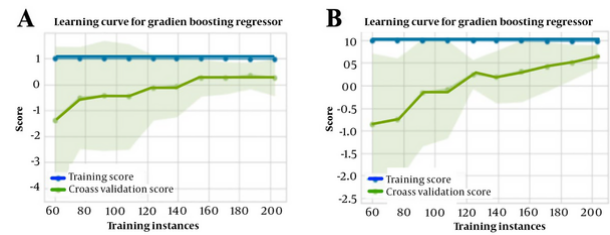
5. Discussion

Immediate antidotal treatment in patients with severe OP poisoning is crucial. The first line of antidotal therapy for OP poisoning includes atropine and pralidoxime (34). In antidote therapy, prescribing the correct dose of the antidote is vital, although the appropriate dose of pralidoxime in patients with OP poisoning remains controversial, with various dosage schedules being employed (20, 35). Several studies have investigated the ideal dose of pralidoxime in OP-poisoned patients, but the results have been inconclusive. For instance, one study reported that a pralidoxime dose of 20.0 ± 12.7 g was more effective than a dose of 7.2 ± 4.1 g, leading to a reduction in the duration of hospitalization and mortality rate (19). Another study found that a pralidoxime dose of 2 g followed by an 8 mg/kg/h infusion was more effective than a dose of 2 g followed by 1 g every 6 hours (20). We hypothesize that an individualized pralidoxime dose, determined based on clinical presentations and laboratory parameters, might be helpful in these cases.

Machine learning techniques enable healthcare providers and researchers to leverage large amounts of patient data to make precise and individualized dose predictions. By tailoring treatment plans to the unique characteristics of each patient, machine learning can

contribute to improved treatment outcomes, reduced adverse effects, and enhanced patient safety. Machine learning algorithms can analyze complex patterns and relationships within patient data to make accurate dose predictions (36). For instance, in one study, researchers used machine learning methods to develop a predictive model for determining the appropriate dosage of lapatinib in patients with metastatic HER2(+) breast cancer, utilizing real-world data and applying both machine learning and deep learning techniques (29). Another study reported an optimal dosing algorithm for vancomycin in patients with MRSA and other gram-positive bacterial infections, developed using machine-learning methods (31). Asiimwe et al. assessed the performance of 21 machine-learning algorithms in predicting stable warfarin doses in sub-Saharan Black-African patients (37).

In this study, we applied a machine learning technique for the first time to predict pralidoxime doses in patients poisoned by OPs based on demographic profiles, clinical symptoms, and laboratory parameters. We employed two different methods for this purpose. The first method, classification, grouped patients into two categories based on the pralidoxime dose: Either low dose (< 14000 g) or high dose (≥ 14000 g). In the second method, after feature scaling using the standardization technique, the pralidoxime dose was included in the machine-learning model as a continuous variable. A total of 35 features were selected for both the classification and regression methods. The following features were among the top ten in both methods: Age, muscular weakness, ALT, AST, BUN, and initial PChE level. Apart from these shared features, in the classification method, the last measured level of PChE (last measurement within the first 24 hours of hospitalization), ALP, PCO_2-VBG, and the amount of consumed toxin was among the top ten predictors of pralidoxime. In the regression method, additional top predictors included HCO3-VBG, received a bolus of atropine, pulmonary rale, and PH-VBG.

Many of the features selected in this study overlap with those identified in our previous study, which examined predictors of OP poisoning severity (38). The AChE enzyme prevents the buildup of the neurotransmitter ACh at various muscarinic and nicotinic sites in the body by hydrolyzing it. This enzyme has both a serine site and an anionic site. The OP molecule attacks the serine site located within the active site of the enzyme. As a result, through an irreversible interaction, the serine site is phosphorylated, and a strong covalent bond is formed, leading to the inactivation of the enzyme's active site. Pralidoxime functions as a reactivator of AChE by attaching to the enzyme's anionic site, close to the previously attached OP molecule at the serine site. The pralidoxime molecule sacrifices itself by becoming phosphorylated instead of the enzyme since it has a higher affinity for phosphorylation by OP agents than the enzyme's serine site. Consequently, the OP molecule detaches from the enzyme and forms an OP-pralidoxime complex, which is then hydrolyzed. This process results in enzyme reactivation (39). The main effect of pralidoxime is the restoration of ACh esterase at nicotinic sites in the body, alleviating symptoms such as muscle weakness, fasciculations, and paralysis (40). According to our results, muscular weakness was one of the most significant features in predicting the dose of pralidoxime, selected in both the classification and regression methods. Other predictors of pralidoxime dosage are also features directly related to the severity of organophosphorus poisoning and can be used to predict the dosage of pralidoxime in these patients.

In the classification method among different machine learning algorithms, the random forest classifier demonstrated the strongest performance, with an AUC value of 98.6%. In the regression method, the gradient-boosting regressor showed the strongest performance, with an R^2 value of 0.65. Both the random forest classifier and the gradient boosting regressor are decision-tree-based machine learning algorithms. Algorithms utilizing decision trees demonstrate high efficacy in predictive modeling, especially for small-to-medium structured datasets with substantial missing data (38).

The novelty of this study lies in the utilization of machine learning methodology to forecast the optimal dosage of pralidoxime for individuals affected by OP poisoning. This investigation marks the inaugural development of a machine learning-based predictive model for pralidoxime dosage, employing two distinct approaches: Classification and regression. The strength of the study lies in the use of machine learning methods, which offer numerous advantages such as enhanced accuracy, efficiency, and decision-making capabilities. Nevertheless, the study is subject to several limitations, notably the small sample size and the retrospective nature of the data, which led to a considerable amount of missing data in the dataset. Additionally, the absence of an external validation cohort and the recruitment of patients solely from a single hospital further constrain the study. Thus, to obtain confirmatory results, a more robust multicenter study with a larger sample size is imperative.

5.1. Conclusions

Machine learning-based prediction algorithms can be utilized to anticipate the appropriate dosage of pralidoxime for patients suffering from organophosphorus (OP) poisoning. Through the application of feature selection techniques, age, HCO_3-VBG, received bolus of atropine, and AST were identified as the most significant predictors of pralidoxime dosage in the regression method. The gradient-boosting regressor emerged as the most effective algorithm with the highest predictive performance. In the classification method, muscular weakness, the last measured level of PChE, BUN, ALP, and AST were determined to be the most crucial predictors of pralidoxime dosage, with the random forest classifier demonstrating the best predictive performance. These algorithms have the potential to contribute to the development of a clinical decision support system for the precise individualized dosing of pralidoxime in OP poisoning cases. Nevertheless, further research with a larger sample size is imperative to substantiate these findings.

Acknowledgements

Footnotes

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Table 1. Characteristics of Previous Studies Investigating the Effectiveness of Pralidoxime in Patients with Organophosphates Poisoning [a]

Authors	Study	Country, Year	Number of Patients	Sex	Age (y)	Pralidoxime Dosage	Outcome
Pawar et al. ([14])	RCT	India, 2006	200, poisoning by anticholinesterase pesticide	Male; control group: 52; study group: 57	Control group: 29 (22 - 35); Study group: 28 (22 - 33)	Control group: 2 g loading dose over 30 min, then a bolus dose of 1 g/4 h for 48 h; study group: 2 g loading dose over 30 min, then a constant infusion of 1 g/h for 48 h.	Patients in the study group required less atropine, a short duration of ventilatory support, and less frequency of intubation.
Syed et al. ([16])	RCT	India, 2015	100 patients with OP poisoning	Sex ratio (male:female); control group: 1:1.56; study group: 1:1.62	Control group: 28.2 ± 9.9; study group: 29.1 ± 10.9	Control group: Received I.V saline; study group: (30 mg/kg loading dose over 30 min followed by 8 mg/kg/h continuous infusion for a maximum of 7 days	There was no statistically significant difference between the two groups in terms of mortality, hemodynamic parameters, atropine requirements, duration of ventilation, and ICU stay
Eddleston et al. ([11])	RCT	Sri Lanka, 2009	235 patients with OP poisoning	Male; control group: 92 (80.7); study group: 96 (79.3)	Control group: 29.5 (23 - 42); study group: 31 (22 - 48)	Control group: Normal saline infusion; study group: 2 g loading dose over 20 min, then a constant infusion of 0.5 g/h until 7 days	Mortality was non-significantly higher in patients receiving pralidoxime, and the need for intubation was similar in both groups
Thunga and Pandey ([18])	Cross-sectional, nonrandomized observational study	India, 2013	256 OPs poisoned patients	Sex ratio (male: female): 2.3:1	Majority of patients were in the age group of 21 - 30 years	Control group: Normal saline infusion; study groups: Intermittent (1 g/q8h), continuous infusion (500 mg/h), continuous infusion (1 g/h)	The incidence of intermediate syndrome, number of ventilation days, total atropine requirement, number of hospitalization days, and mortality rate significantly reduced in continuous infusion of pralidoxime at 500 mg/hour
Due ([19])	Comparative study	Vietnam, 2014	Control group: 54; study group: 108	Male; control group: 30 (55.6); study group: 64 (59.3)	Control group: 25.5 ± 10; study group: 29.5 ± 14.2	Control group: Received a mean total dose of 7.2 ± 4.1 g; study group: Received a mean total dose of 20.0 ± 12.7 g	In the study group, patients received significantly lower doses of atropine and required a shorter duration of hospital stay, and the mortality rate was lower than the control group
Mahesh et al. ([20])	Randomized open-labeled prospective study	India, 2013	Control group: 45; study group: 37	Male:female, control group: 35:10; study group: 21:16	Control group: 30.1 ± 7.3; study group: 31.3 ± 8.9	Control group: 2 g bolus followed by 1g/6 h; study group: 2	

Authors	Study	Country, Year	Number of Patients	Sex	Age (y)	Pralidoxime Dosage	Outcome
						mg/kg/h infusion	Duration of mechanical ventilation, mean dosage of atropine administered, and incidence of intermediate syndrome were significantly lower in the study group than in the control group
Chaudhary et al. (21)	Case-control study	India, 2013	Control group: 35; study group: 35	Male:female, control group: 25:10; study group: 24:11	Control group: 24.80 ± 8.3; study group: 25.17 ± 9.2	Control group: -; study group: 30 mg/kg body weight in 200 mL of normal saline over 30 min followed by 2.0 g in 200 mL of normal saline over 30 min, at 6 h intervals for initial 72 h	There was no statistically significant disparity observed between the two groups in relation to the total amount of atropine administered, necessity for intubation, average length of hospitalization, and mortality rate.
Cherian et al. (22)	RCT	India, 2005	Control group: 11; study group: 10	NA	NA	Control group: Normal saline infusion; Study group: PAM infusion of 12 g/day for 3 days in severe cases and 4 g/day for 3 days in moderate cases	There was no difference between the treatment and placebo groups in relation to the necessity for intubation, average length of hospitalization, and mortality rate.
Cherian et al. (23)	RCT	India, 1997	Control group: 55; Study group: 55	Male, control group: 34 (62); study group: 41 (75)	Control group: 26.5 ± 10.3; study group: 28 ± 10.1	Control group: Normal saline infusion for 3 days; study group: Infusion of 12 g over 3 days	The requirement of ventilator support (37 vs. 22), the incidence of an intermediate syndrome (36 vs. 19), and the mortality rate (16 vs. 3) were higher in the study group than in the control group
Banerjee et al. (24)	Open-label, parallel-group clinical study	India, 2011	Control group: 30; study group: 30	Male, control group: 11 (37); study group: 14 (47)	Control group: 34.3 ± 8.8; study group: 34.6 ± 9.8	Control group: -; study group: a dose of 0.5 - 1 g/6 h	The mortality rate, requirement of ventilator, and duration of hospital stay in the two groups failed to show any statistically significant difference.
Banerjee et al. (25)	Open-label, parallel-group, randomized clinical trial	India, 2014	Control group: 60; study group: 60	Male, control group: 26 (43); study group: 23 (38)	Control group: 34.3 ± 8.8; study group: 34.6 ± 9.8	Control group: -; study group: A dose of 1 g every 6 hours for a period of 5 days	Pralidoxime therapy did not offer any appreciable benefit over atropine alone in terms of reducing mortality and ventilator requirement. Patients in the study group experienced

Authors	Study	Country, Year	Number of Patients	Sex	Age (y)	Pralidoxime Dosage	Outcome
							longer duration of hospital stay

^a Values are expressed as No. (%), mean ± SD or median (IQR) unless otherwise indicated.

Table 4. The Study Sample's Descriptive Characteristics [a]

Variables	Pralidoxime Dose		Total (n = 325)	P-Value
	Low Dose (n = 172)	High Dose (n = 153)		
Sex				0.06
Male	96	69	165	
Female	76	84	160	
Age	33 (25)	31 (22)	-	0.092
Time to hospitalization	4 (10)	4 (7)	-	0.332
Sialorrhea				0.000
No	160	135	295	
Yes	12	18	30	
Bradycardia				0.370
No	169	152	321	
Yes	3	1	4	
Rales				0.000
No	153	111	264	
Yes	171	153	324	
Bronchospasm				0.467
No	116	97	213	
Yes	56	56	112	
Intubation				0.763
No	121	105	226	
Yes	51	48	99	
Incontinence				0.138
No	166	142	308	
Yes	6	11	17	
Fasciculation				0.000
No	160	122	282	
Yes	12	31	43	
Muscular weakness				0.000
No	141	47	188	
Yes	31	106	137	
Paralysis				0.000
No	172	140	312	
Yes	0	13	13	
Tachycardia				0.738
No	88	75	163	
Yes	84	78	162	
Confusion				0.270
No	98	96	194	
Yes	74	57	131	
Lethargy				0.180
No	170	153	323	
Yes	2	0	2	
Coma				0.380
No	127	106	233	
Yes	45	47	92	
Agitation				0.017
No	172	148	320	
Yes	0	5	5	
Seizures				0.621
No	167	147	314	

Variables	Pralidoxime Dose		Total (n = 325)	P-Value
	Low Dose (n = 172)	High Dose (n = 153)		
Yes	5	6	11	
ICU admission				0.284
No	95	75	170	
Yes	77	78	155	
The amount of toxin consumed	90 (120)	150 (150)	100	0.00
GCS	15 (7)	15 (7)	12.5	0.589
Cholinesterase level first	305 (971)	317 (1114)	316.5	0.787
Cholinesterase level last	458 (835)	715 (1898)	583.50	0.172
PH-VBG	7.35 (0.11)	7.34 (0.13)	7.345	0.291
PCO$_2$-VBG	38.4 (14.4)	41.5 (11.7)	40.3	0.001
HCO$_3$-VBG	19.6 (4.7)	20.4 (5.2)	20.4	0.346
Cr	1.2 (0.3)	1.2 (0.3)	1.2	0.005
BUN	28 (18.5)	33 (15)	31	0.002
AST	26 (16.3)	25 (12)	25	0.595
ALT	19 (13)	17 (9)	18	0.017
ALP	204 (79)	178 (79)	192	0.002
Bulos of atropine	0.5 (1)	1 (1)	0.5	0.593

[a] Values are expressed as No. or median (IQR).