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Factors associated with outcomes in organophosphate and carbamate poisoning: a retrospective study

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Abstract

Organophosphate and carbamate (OPC) poisoning is a major global health hazard requiring immediate medical intervention. Atropine (ATR) is an essential antidote in organophosphate and carbamate poisoning, with the inclusion of cholinesterase reactivators and other anticholinergics, namely pralidoxime (PAM) and glycopyrrolate (GPR). This study aimed to compare the efficacy of various treatment regimens and identify the factors affecting mortality. The data of patients presented at the emergency unit with the consumption of OPC compounds between the years 2013 and 2017 were retrospectively reviewed. The study population was then categorized into four treatment patterns (1) ATR alone, (2) ATR and PAM, (3) ATR and GPR, (4) ATR, PAM and GPR. The outcome of the patients was assessed in terms of survival, intubation, ICU days, and days of ventilation and hospitalization. Univariate and multivariate analyses were performed to investigate the risk factors associated with mortality and odds ratio (OR). A total of 441 patients were included in the study, of which 69.16% were males, and 375 patients survived. Consumption of poison with a suicidal intention was reported in 98.19% of the patients, and the treatment with ATR and PAM (42.86%) was observed to have lower days of ventilation in comparison to the treatment with ATR and GPR ($p = 0.003$). Patients requiring intubation were also lowest in the group treated with ATR and PAM (27.51%). The age group of > 50 years (OR 4.275 [CI 2.179–8.387]), male gender (OR 2.608 [CI 1.258–5.406]), and the treatment pattern with ATR, PAM and GPR (OR 2.233 [CI 1.002–4.040]) were independently associated with mortality. In summary, male gender, elderly population, and treatment patterns followed adversely affected the outcome in patients with OPC poisoning.

Keywords Atropine · Carbamate · Glycopyrrolate · Organophosphate · Older age · Pralidoxime

Introduction

Organophosphate and carbamate (OPC) poisoning occupy a major share of poisoning with the intention of self -harm. It is one of the major public health issues in Asian countries. In developing countries like India that rely mostly on agriculture, the ease of availability and an extensive use of pesticides in horticulture have made this issue portentous. Worldwide, the number of organophosphate pesticide intoxications alone are estimated to be as high as 3,000,000 per year, and the causalities and deaths are about 300,000 per year [1].

OPC compounds, being highly lipid soluble, easily penetrate the skin and gastric mucosa, and are thereby rapidly distributed to tissues and penetrate the blood–brain barrier to act on the CNS system [2]. In the case of OPC poisoning, the inhibition of the acetylcholinesterase activity by the phosphorylation of acetylcholinesterase renders the enzyme inactive, thereby causing the accumulation of acetylcholine at the synapse, leading to the cholinergic toxidrome. The symptoms such as miosis, bronchospasm, increased secretions, vomiting, arrhythmia, fasciculation, and respiratory failure are the results of enhanced muscarinic and nicotinic stimulation [3, 4]. The OPC poisoning is usually determined

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by verifying the acetylcholinesterase and pseudocholinesterase levels. However, acetylcholinesterase assay requires special precautions during the sample collection, such as rapid dilution and cooling, to avoid ex vivo reactions occurring overtime in acute poisoning [3]. Minor difficulties in the auto analyzer [5] also add up to the unavailability of the analysis in developing nations [6].

Atropine (ATR) remains the mainstay in the treatment of OPC poisoning with its anticholinergic actions and its ability to penetrate the CNS. It competitively inhibits muscarinic acetylcholine receptors and prevents further stimulation. The dose of atropine usually varies from patient to patient. The patients were treated until the suggestive end-points of atropinization such as having a clear chest on auscultations, the absence of secretions, heart rate > 100 bpm, dilation of the pinpointed pupil and dry axillae were achieved. A systematic review by Eddleston et al. reveals that there are more than 30 different dosing regimens in place, and the physicians had to administer a high dose of atropine to attain atropinization, which led to ATR toxicity [7]. ATR toxicity leads to extended hospitalization and associated complications [8].

Apart from atropine, antidotes such as oximes and glycopyrrolate (GPR) were considered based on the patient's condition. Pralidoxime (PAM), belonging to the oxime group, was reported to reactivate acetylcholinesterase inhibited by the organophosphate compounds. The efficacy and addition of PAM to the treatment regime in organophosphate poisoning is still debated and unconvincing [3]. The usage of PAM is usually avoided in carbamate poisoning unless the poison is unknown and the patient is presented with cholinergic toxidrome [9]. Glycopyrrolate being a Quaternary Ammonium anticholinergic agent exerts its peripheral antimuscarinic actions and is considered to be more potent than ATR [10]. A retrospective study by Arendse et al. suggests that co-administration of GPR with ATR may improve the efficacy of the treatment in comparison to previous studies pertaining to the treatment with atropine alone at the same hospital [11, 12]. However, a previously similar retrospective study at our hospital suggested an increased need for ventilation and intubation with the combined usage of ATR and GPR [13].

We hereby analyzed the data obtained from Kasturba Hospital, Manipal, to determine the effectiveness of various treatment patterns and their outcomes.

Materials and methods

Study setting and data sources

The hospital is a tertiary care centre situated in South India catering to the admission of 78,000 rural population per year. Ethical clearance was obtained from the Institutional Ethics Committee of Kasturba Hospital, Manipal Academy of Higher Education, Manipal, for the disclosure of the records. (IEC: 590/2017). A retrospective descriptive analysis study was performed on the patients identified from January 2013 to September 2017.

The diagnosis was made on the history of poison consumption and clinical characteristics of the patients. The serum pseudocholinesterase levels were assessed to determine OPC poisoning. Though red blood cell cholinesterases are the gold standard in the estimation of OPC poisoning, the facilities to measure were not available at the hospital. The pseudocholinesterase levels were determined colorimetrically based on the assay published by Schmidt et al. using Hitachi Roche Cobas C702 [14]. The reference range followed at our hospital is 5300–12,000 U/L.

Demographic details like age, gender, occupation, social history, and patient outcomes were collected. Information regarding the presence of any psychological illness, the typical route of exposure and estimated quantity of the pesticide ingested were retrieved from the files on a structured proforma. The intention of poisoning was categorized into suicidal, accidental, and homicidal as noted in the medical records of the patients. Most of the patients presented were referred cases from the local hospital, and hence, the pre-hospitalization period was categorized to more or less than 24 h after the consumption of poison. The patients were categorized into four categories based on the treatment regimen followed (1) atropine alone, (2) atropine and pralidoxime, (3) atropine and glycopyrrolate, (4) atropine, pralidoxime and glycopyrrolate. The majority of the severely ill and unresponsive patients were usually assigned the treatment with atropine, pralidoxime and glycopyrrolate at the discretion of the physician in a life-saving approach. Patients who usually required intubation, ventilation and large doses of atropine for achieving atropinization with declining clinical parameters were considered as severely ill and GPR was added as an additional antidote. The severity of poisoning was evaluated in accordance to the WHO International Programme on Chemical Safety [15]. The severity was assigned by considering the most severe signs and symptoms and graded between 0 and 4. Total ATR administered to the patient was calculated by adding all the doses from the day of admission to the day of discharge including the infusion and intermittent dosing. The effectiveness of each treatment pattern was assessed with primary and secondary outcomes.

Study population

The records of 604 patients presented at the emergency ward with the diagnosis of OPC poisoning were identified electronically using the ICD code T60.0. The data was retrospectively retrieved from medical records manually. The

majority of patients were referred from the local hospitals. The follow-up information after their discharge was not considered. A total of 441 adult patients were considered eligible for the study. An exclusion criteria comprised all patients less than 18 years of age, patients with missing data in their treatment regime, patients discharged against medical advice, and patients with mixed poisoning with varied chemicals such as phenol and rodenticides owing to their dissimilar treatment pattern and overall morbidity and mortality (Fig. 1).

Outcomes

Patients diagnosed with OPC poisoning are usually admitted to the ICUs. Primary outcomes were assessed in terms of recovery status as either survived or expired. The survived category included the patients completely recovered and discharged. The secondary outcomes were assessed in terms of days of intubation, ICU days, days on ventilation and days of hospitalization as shown in Table 2.

Statistical analysis

All statistical analyses were carried out using the SPSS 20.0 package. The values for continuous variables are expressed as mean and standard deviation (SD); values for categorical variables are expressed as frequency and percentages. The data of days in ICU, days of ventilation, days of hospitalization, pseudocholinesterase levels, and dose of atropine, pralidoxime, glycopyrrolate utilized is represented in the median and quartile values. Kruskal–Wallis's test was applied for the comparison of the four treatment groups followed by the Mann–Whitney U test for pairwise comparison. With the Bonferroni correction for pair wise comparison, $p < 0.05$ was divided between six groups (0.05/6) and a value of $p \leq 0.0084$ was considered statistically significant for the days of ventilation, days in ICU and the dose of atropine utilized (Table 4). Univariate followed by multivariate regression was used to identify risk factors associated with deterioration of medical conditions in patients poisoned with OPC, and odds ratio (OR) was calculated. Variables significantly
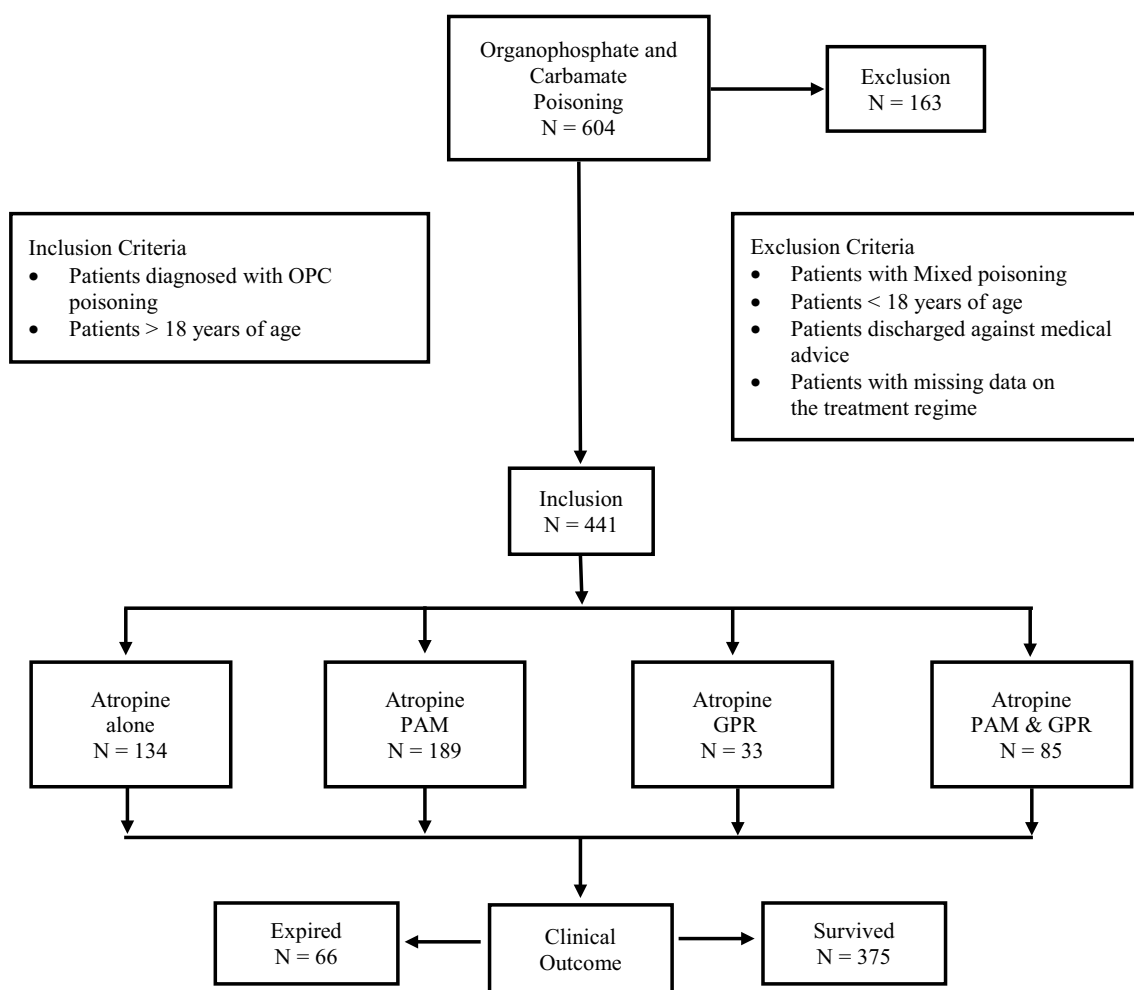

Fig. 1 Patient flow diagram. *PAM* pralidoxime, *GPR* glycopyrrolate

associated in OPC poisoning in the univariate analysis were selected as independent variables in the multivariate analysis. The data of patients with unknown poisoning agents and poisoning agents having less than an adequate number of patients (<10) were not included in the regression analysis. Age stratified into three groups to determine the risk, and *p* value <0.05 was considered as statistically significant.

Results

Demographics

A total of 441 eligible patients were admitted to the emergency ward with a history of OPC poisoning. The mean age of the study population was 36.81 ± 14.91 years. Gender distribution shows a substantial variation between the male and female population in the study, with males being 305 (69.16%) and females 136 (30.84%) (Table 1). Male population was strikingly high (95.28%) in the patients observed with a history of alcohol consumption.

There were no cases of poisoning by inhalational or dermal exposure. The consumption of poison with a suicidal intention was widely observed (98.19%), followed by

Table 1 Demographic data of patients

Total number of patients	N = 441, n (%)
Age, mean (SD)	36.81 (14.91)
Male	305 (69.16)
Female	136 (30.84)
Social history	
Alcoholism (% of males)	106 (95.28)
Intention of poisoning	
Suicidal	433 (98.19)
Accidental	6 (1.36)
Homicidal	2 (0.45)
Comorbidities	
Psychological illness	73 (16.55)
No psychological illness	368 (83.45)
Occupation	
Daily wagers	120 (27.21)
Farmers	102 (23.13)
Housewives	94 (21.32)
Salaried	49 (11.11)
Students	37 (8.39)
Business	15 (3.40)
Others	24 (5.44)
Clinical outcome	
Survived	375 (85.03)
Expired	66 (14.97)

n number, % percentage

accidental consumption (1.36%). The study population comprised a majority of daily wagers (120) (27.21%), followed by farmers (102) (23.13%), and housewives (94) (21.32%) (Table 1).

There were 13 OPC compounds found in our study. Chlorpyrifos was the most consumed poison in 108 (24.49%) of the total OPC admissions during the study, while in 136 (30.84%) patients the poison ingested was not specified. The patients poisoned with ethion 6, malathion 4, dichlorvos 3 and propoxur 3 were not considered for the univariate analysis (Table 5).

Patients admitted with OPC poisoning were grouped into one of the four treatment categories.

The four treatment groups were:

- ATR alone treatment group: This group consisted of 134 (30.39%) subjects.
- ATR and PAM treatment group: This group consisted of 189 (42.86%) subjects.
- ATR and GPR treatment group: This group consisted of 33 (7.48%) subjects.
- ATR, PAM and GPR: This group consisted of 85 (19.27%) subjects and the treatment included usage of all the three drugs.

Primary outcomes

Primary outcomes of various treatment regimen were assessed in terms of the patient's condition at discharge (survived or expired). It was observed that the patients treated with ATR and PAM has a better clinical improvement 167 (88.36%) patients than the patients treated with other regimens. A significant difference ($p = 0.041$) was observed between the treatment groups, and the patient group treated with ATR, PAM and GPR had the least improvement 64 as the group consisted of a majority of severely ill patients (75.29%) (Table 2).

Secondary outcomes

The secondary outcomes of different treatment regimens were assessed in terms of intubation, ICU days, days on the ventilator, and hospitalization days. Hospitalization days were higher in the group treated with ATR, PAM and GPR, whereas the group treated with ATR and PAM had the least number of days of ICU and ventilator (Table 2). The group treated with ATR and PAM was also observed to have the least intubation (27.51%). A significant difference in the rate of intubation ($p = 0.001$) was observed between the treatment groups. Classification by Poison Severity Score revealed a significant difference in the allotment of minor ($p < 0.001$) and fatal categories ($p = 0.041$) (Table 2). The proportion of fatal patients was higher in the male population and in

Table 2 Outcomes of the patients, serum pseudocholinesterase levels and atropine utilization

Parameter	Treatment pattern				*p* value
	ATR alone N = 134 n (%)	ATR and PAM N = 189 n (%)	ATR and GPR N = 33 n (%)	ATR, PAM and GPR N = 85 n (%)	
Primary outcome					
Survived	115 (85.82%)	167 (88.36%)	29 (87.88%)	64 (75.29%)	0.041[c]
Expired	19 (14.18%)	22 (11.64%)	4 (12.12%)	21 (24.71%)	
Secondary outcomes					
Intubation	55 (41.04)	52 (27.51%)	18 (54.55%)	43 (50.59%)	< 0.001[c]
ICU days, mean (SD)	9.49 (6.04)	9.16 (5.72)	11.63 (5.95)	11.51 (7.80)	
ICU days, median (95% CI)	8 (5–12)	8 (6–11)	12 (7–15)	10 (6–15)	0.022[a]
Days on ventilator, mean (SD)	9.15 (6.72)	8.80 (7.28)	11.84 (4.18)	10.71 (7.41)	
Days on ventilator, median (95% CI)	8 (3.25–13)	8 (4, 11)	12 (7, 14)	9.5 (5–14.75)	0.030[a]
Hospitalization days, mean (SD)	13.11 (8.33)	12.39 (7.17)	13.79 (7.68)	15.16 (9.92)	
Hospitalization days, median (95% CI)	11 (8.75–16)	11 (8–15.5)	13 (7–19)	13 (8.5–19)	0.168[a]
Poison Severity Score					
Minor	78 (58.21)	96 (50.79)	21 (63.64)	25 (29.41)	< 0.001[c]
Moderate	25 (18.66)	52 (27.51)	7 (21.21)	24 (28.24)	0.237[c]
Severe	12 (8.96)	19 (10.05)	1 (3.03)	15 (17.65)	0.077[c]
Fatal	19 (14.18)	22 (11.64)	4 (12.12)	21 (24.71)	0.041[c]
Serum pseudo-cholinesterase levels					
Median (95% CI) (IU/L)	601.5 (147.5–3316.75)	258 (171–2767)	742 (123–3184)	242 (160–984)	0.530[a]
Total dosage of ATR utilized					
Median (95% CI) (mg)	454 (146.5–1362.54)	491.3 (166.4–1281.58)	687 (106.3–1971)	864.55 (304.2–2010.4)	0.016[a]
Total dosage of PAM utilized					
Median (95% CI) (gm)	NA	4 (3–6)	NA	6 (4–7)	< 0.001[b]
Total dosage of GPR utilized					
Median (95% CI) (mg)	NA	NA	10.28 (3.6–65.2)	21.2 (7.8–63.3)	0.276[b]

n number, *%* percentage, *SD* standard deviation, *CI* confidence interval, *mg* milligram, *gm* gram, *IU/L* international units per litre, *NA* not applicable, *ATR* atropine, *PAM* pralidoxime, *GPR* glycopyrrolate

[a]Kruskal–Wallis test

[b]Mann–Whitney pair-wise comparison test

[c]Chi-Square test

the patients over the age of 50 in the Poison Severity Score (Table 3).

The days of ventilation were analyzed using the Kruskal–Wallis test and Mann–Whitney's pair-wise comparison test to assess the effectiveness of various treatment patterns. The results of the Kruskal–Wallis test revealed that the median days of ventilation varied significantly among the various treatment regimen ($p = 0.030$) (Table 2).

- Pair-wise comparison test reported a significant difference ($p = 0.003$) in the days of ventilation between patients treated with ATR and PAM versus ATR and GPR (Table 4).

Although the Kruskal–Wallis test reported the existence of a significant difference in the days of ICU ($p = 0.022$)

Table 3 Poison Severity Score across gender and age groups

Factor	Poison Severity Score			
	Minor 220 n (%)	Moderate 108 n (%)	Severe 47 n (%)	Fatal 66 n (%)
Age				
18–30 years	129 (58.64)	44 (40.74)	14 (29.79)	18 (27.27)
31–50 years	72 (32.73)	35 (32.41)	19 (40.43)	20 (30.30)
50 years above	19 (8.64)	29 (26.85)	14 (29.79)	28 (42.42)
Gender				
Female	78 (35.45)	33 (30.56)	15 (31.92)	10 (15.15)
Male	142 (64.55)	75 (69.44)	32 (68.08)	56 (84.85)

n number, *%* percentage

Table 4 Comparison of days of ventilation, days in ICU and dosage of ATR utilized between various treatment groups

Comparison of treatment regimen[a]	Days of ventilation p value[b] ≤ 0.0084	ATR dosage utilized p value[b] ≤ 0.0084	Days in ICU p value[b] ≤ 0.0084
ATR Alone vs ATR and PAM	0.741	0.462	0.775
ATR Alone vs ATR and GPR	0.029	0.615	0.053
ATR Alone vs ATR and PAM and GPR	0.223	0.002[c]	0.056
ATR and PAM vs ATR and GPR	0.003[c]	0.947	0.019
ATR and PAM vs ATR, PAM and GPR	0.126	0.006[c]	0.018
ATR and GPR vs ATR, PAM and GPR	0.125	0.156	0.567

[a]Mann–Whitney pair-wise comparison test

[b]Bonferroni correction for pair wise comparison $p < 0.05$ was divided between six groups (0.05/6) and a value of $p \leq 0.0084$ is considered statistically significant

[c]Statistically significant

(Table 2), and further analysis by the Mann–Whitney test revealed no significant difference in the pair-wise comparison (Table 4).

The results of the univariate regression analysis are summarised in Table 5. Variables of poison type, prehospitalization period, and the type of decontamination were analyzed to identify a possible association with the mortality of the patients. Variables, namely, chlorpyrifos, methyl parathion, phorate, patients presenting to the emergency unit 24 h post poisoning, and decontamination involving activated charcoal had an OR > 1. However, they were not statistically significant. Older age, gender and treatment pattern followed were independently associated with mortality in OPC poisoning (Table 6).

Atropine utilization

ATR remains the cornerstone in the treatment of OPC poisoning. It was present in all the four treatment patterns of comparison and was administered to all the patients presented with OPC poisoning. The median ATR dose was found to be higher in the group treated with ATR, PAM and GPR and the least in the group treated with ATR alone (Table 2).

The total ATR utilized was analyzed using the Kruskal–Wallis test and the Pair-wise comparison test to assess the variation of ATR usage across the treatment patterns. The results of the Kruskal–Wallis test revealed that the median of the total ATR utilized varied significantly between various groups ($p = 0.016$). The Pair-wise comparison test

Table 5 Univariate analysis of factors affecting mortality in OPC poisoning patients

Factor	Survived 375 n (%)	Expired 66 n (%)	OR (95% CI)	p value
Poisoning agent				
Chlorpyrifos (OP)	91 (24.27)	17 (25.76)	1.083 (0.594–1.973)	0.795
Parathion methyl (OP)	13 (3.47)	5 (7.58)	2.282 (0.786–6.631)	0.129
Phorate (OP)	27 (7.20)	5 (7.58)	0.914 (0.392–2.850)	0.914
Monocrotophos (OP)	22 (5.87)	3 (4.55)	0.764 (0.222–2.629)	0.670
Quinalphos (OP)	26 (6.93)	6 (9.09)	1.342 (0.530–3.399)	0.535
Dimethoate (OP)	17 (4.53)	4 (6.06)	0.592 (0.442–4.173)	0.592
Triazophos (OP)	11 (2.93)	1 (1.52)	0.521 (0.065–4.011)	0.521
Profenofos (OP)	18 (4.80)	2 (3.03)	2.736 (0.140–2.736)	0.528
Carbofuran (C)	20 (5.33)	1 (1.52)	0.273 (0.036–2.070)	0.209
Pre-hospitalization period				
< 24 h	280 (74.67)	51 (77.27)	1.154 (0.620–2.146)	0.652
> 24 h	95 (25.33)	15 (22.73)	0.867 (0.466–1.613)	0.652
Type of decontamination				
Gastric lavage	24 (6.40)	3 (4.55)	0.696 (0.204–2.382)	0.564
Activated charcoal	19 (5.07)	7 (10.61)	2.217 (0.893–5.504)	0.086

OP organophosphate, *C* carbamate, *OR* odds ratio

Table 6 Adjusted OR and 95% CI for the factors associated with mortality in OPC poisoning patients

Factor	Survived 375 n (%)	Expired 66 n (%)	Adjusted OR (95% CI)	p value
Age				
18–30 years	187 (49.87)	18 (27.27)	Reference category	
31–50 years	126 (33.60)	20 (30.30)	1.455 (0.732–2.892)	0.285
50 years above	62 (16.53)	28 (42.42)	4.275 (2.179–8.387)	< 0.001[a]
Gender				
Female	126 (33.60)	10 (15.15)	Reference category	
Male	249 (66.40)	56 (84.85)	2.608 (1.258–5.406)	0.010[a]
Treatment pattern				
ATR and PAM	167 (44.53)	22 (33.33)	Reference category	
ATR alone	115 (30.67)	19 (28.79)	1.123 (0.567–2.221	0.740
ATR and GPR	29 (7.73)	4 (6.06)	0.757 (0.232–2.468	0.644
ATR, PAM and GPR	64 (17.07)	21 (31.82)	2.233 (1.002–4.040)	0.049[a]

OR odds ratio, *ATR* atropine, *PAM* pralidoxime, *GPR* glycopyrrolate

[a]Statistically significant $p < 0.05$

revealed a significant difference in the total ATR administered between patient groups treated with ATR alone versus ATR, PAM and GPR, and ATR and PAM versus ATR, PAM and GPR at $p = 0.002$ and $p = 0.006$, respectively (Table 4).

Pralidoxime utilization

Pralidoxime was utilized in two treatment arms, namely, ATR and PAM and ATR, PAM and GPR. The median PAM utilized was found to be higher in the group treated with ATR, PAM and GPR. The Pair-wise comparison test revealed a significant difference in the total PAM administered between patient groups at $p < 0.001$ (Table 2).

Discussion

Consumption of poison with the intention of suicide was widely observed in the South Indian population [16, 17]. A male to female ratio of 2.2:1 was found to support male preponderance in poisoning by other studies [18]. The prevalence can be attributed to males, as they comprise the main working group in the farms, and the stress associated with crop failures, unpredictable monsoons and economic burden as well relies on them [19–21]. The mean age in our study population was about 36.81 ± 14.91, similar to the study by Coskun et al. with a mean age of 39 ± 16 years [22]. The self-poisoning was considerably observed in daily wagers and farmers who have easy access to the chemicals [23], and chlorpyrifos was the pesticide mostly consumed in our population owing to its wide usage in countries like India and Sri Lanka [24, 25]. The Insecticides Act, 1968, was enacted for the sale, transport and distribution of insecticide in order to prevent the risk to human beings. However,

the provisions of the Act are restricted to the definition of 'Insecticide' and are insufficient to regulate substances being used as pesticides. The control measures should include the establishment of poison information centres, safe storage of pesticides at the community level, including investments to improve quality, affordability, and accessibility of health care in proximities of affected communities. More importantly, actions to improve the mental health of farmers and suggesting alternatives to pesticides should be taken up by the government [26]. A retrospective study by Al Mutairi et al. in the Saudi Arabian population reported that mental illness could be a driving force for the consumption of OPC poison, wherein 10.98% of the study population admitted with OPC poisoning was suffering from a psychiatric illness. A similar pattern was revealed in our study with 73 (16.55%) patients reporting a history of a psychiatric illness [27].

The treatment regimen of OPC varies according to the hospital setting. Our study observed four different treatment regimens, and is the first of its kind in the comparison of four different regimens, and it elucidates the effectiveness of each treatment pattern. Though atropine is predominantly used in the treatment of OPC poisoning with its wide antimuscarinic effects, its inability to act on nicotinic receptors [28] has led to the inclusion of oximes to the treatment regime.

Pralidoxime belongs to the class of oximes. Though it has proved its efficacy in the in vitro studies and is suggested in the treatment algorithms [29], its use in the clinical setting has always been a debate with varying outcomes as suggested by Syed S et al. in a randomized controlled trial [30]. The efficacious PAM usage as an adjunct therapy to atropine in OPC poisoning has been suggested by Worek et al. [31]. and Kurtz et al. [32]. An aggressive atropinization followed by a continuous PAM usage was found to decrease the overall mortality in a case series of 16 patients with severe OPC

poisoning [33]. The delay in oxime therapy was associated to increased mortality in a retrospective study by Ahmed et al. [34]. Considering the evidence from such individual studies, the usage of PAM in high doses is still recommended in various guidelines for treating patients with moderate to severe OPC poisoning [29, 30, 34, 35]. A recent randomized control study on Indian population suggests the efficacy of PAM when used in high dosages [36]. In our study, the treatment with ATR and PAM was observed to have the highest rate of survival of 88.36%, minimal mortality of 11.64%, and the least hospital duration of 12.39 ± 7.17 compared to other treatment groups. An improvement in the overall outcome by the addition of PAM was reported in a prospective observational study by Baloch et al. [37]. Conversely, a sharp dissent in the usage of PAM was reported in a review by Eddleston et al. [3] and randomized clinical trials by Banerjee et al. [38] and Kamal et al. [39] stating increased mortality in the group treated with ATR and PAM. Theoretically, oximes play a supporting role to atropine by treating the nicotinic symptoms such as progressive muscle weakness leading to peripheral respiratory failure by reactivating the phosphorylated cholinesterase [40].The use of both ATR and PAM can alleviate the symptoms associated with the accumulation of acetylcholine in the CNS such as seizures, altered consciousness, and centrally mediated respiratory failure [40], hence, managing both peripheral and central respiratory symptoms at the time of acute cholinergic crisis. A randomized clinical trial by Cherian et al. [41] and metaanalysis by Rahimi et al. [42] suggest an increased need for ventilation in the patients treated with pralidoxime. However, our study results reported a decreased need for intubation and lower ventilator days in the group treated with ATR and PAM compared to ATR alone and ATR and GPR. The results of the group ATR and PAM could be biased as mentioned in the limitation, as the severely ill and unresponsive patients were started with an inclusion of GPR, thereby, the patients were moved to ATR, PAM and GPR group. There was also no statistically significant difference in the days of hospitalization and days in the ICU between the treatment groups.

Though, GPR was addressed to portray its efficacy when added to the treatment regime according to the case reports and retrospective studies by Choi et al. [43], Arendse et al. [11] and Unnikrishnan et al. [44]. A significant difference ($p = 0.003$) in the median days on ventilation was found between treatments of ATR and PAM versus ATR and GPR with the latter having longer days of ventilation. Overall, there was an increased need for intubation (54.55%) and a longer duration of ICU. Ventilation, ICU, and hospital stay was observed to be longer in comparison with the group treated with ATR alone. These results were corroborated in the retrospective study by Bhandarkar et al. [13] and prospective observational study by Anju N et al. [45]. The results suggest that the inclusion of glycopyrrolate is not advantageous in alleviating the condition of patients with OP poisoning.

The dose of atropine was not reduced when used in combination with pralidoxime and glycopyrrolate, probably due to varying mechanism of actions. A similar observation was noticed in a prospective study by Chaudhary et al. [46] and a non-randomized clinico-therapeutic trial by Chugh et al. [47] wherein, the addition of PAM did not reduce the dosage of atropine. There are various factors such as poison load, delayed hospital admission, declining laboratory parametres and initial treatment that affect the dose of ATR. An individual case series observed an increased utilization of ATR and a longer duration of hospitalization in the severely ill patients unresponsive to the conventional dosage of atropine [48].

The risk factors significantly associated with mortality were older age > 50 years, male gender and the treatment with the combination of ATR, PAM and GPR (Table 6). In older patients, the decreased muscle mass and increased body fat enable rapid distribution and storage of pesticides in the body. Furthermore, the reduced blood flow and decreased renal and hepatic functions delay the elimination of pesticides from the body contributing to poor outcomes [49]. The increased mortality in males can be attributed to the social habits of the male population such as alcoholism, a comorbidity that might have led to poor prognosis. Chronic alcohol consumption can cause difficulties in the prognosis [50],; delirium and tachycardia ascribable to withdrawal further complicates the administration of atropine [51]. The treatment pattern of ATR, PAM and GPR was followed at our study centre on the unresponsive and severely ill patients. The results of this pattern were unpropitious with the highest rate of mortality of 24.71%, decreased survival rate of 75.29%, longer duration of ICU of 11.51 ± 7.80, and the highest mean hospitalization days of 15.16 ± 9.92. This could be as a result of compromising clinical conditions of the patients, and the addition of PAM and GPR was considered as an additional antidote in severely ill patients. Although there was a greater utilization of ATR and PAM with the inclusion of three antidotes in a life-saving approach, the treatment pattern was not beneficial in improving the condition of the severely ill patients and it reported greater mortality.

In summary, pesticide self-poisoning is a major health hazard in India, mostly affecting farmers and daily wagers. Suicidal intention was the predominant reason for the consumption of poison. The majority of patients were males belonging to the reproductive age. ATR is the well-known antidote used for the management of OPC poisoning. The treatment analysis revealed the treatment group with ATR and PAM had reduced intubation and lower days of ICU and ventilation. The study describes the on-going treatment patterns followed, and identifies older age, gender

and treatment pattern as independent risk factors for mortality.

Limitations

Our study did not represent an equal number of patients in each treatment pattern, and the use of ATR, PAM and GPR in a majority of severely ill and unresponsive patients could lead to bias. The information on the poison type, GCS and APACHE scoring, serum OPC concentrations, serial pseudocholinesterase measurement, co-morbidities present, and the treatment provided at the local hospital was compromised, as this was a retrospective study.

Compliance with ethical standards

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