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Research Article

ORGANOPHOSPHATE POISONING- THE MORTALITY DETERMINANTS: A COMPARITIVE COHORT STUDY BETWEEN THE SURVIVED AND SUCCUMBED

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A B S T R A C T

Importance: OP poisoning is a major global health concern. Few research works have focussed on factors determining death.
Objective: We aimed to identify key factors which determine the outcome among OP poisoned patients.
Design: This is a retrospective cohort study comparing age matched OP poisoned patients [Cohort 1(n=100) Fatal outcome versus Cohort 2(n=200) Survived].
Setting and Participants: The study was conducted at Government Villupuram Medical College and Hospital, Southern India. Only moderate and severely Organophosphate poisoned inpatients were included in the study as per Peradeniya OP Scale[5]. The data were collected under 3 heads- Pre-admission, [in hospital] Clinical features and Management factors.
Exposure: Patients who were exposed to OP within the last 24 hours and with signs of toxicity.
Main Outcomes: The only two outcomes studied were death and survival.
Results: Mortality determining pre admission factors were delayed presentation [22 % of Cohort 1 vs 9.5% of Cohort 2, Chi sq 22.24,p <0.001] and alchohol co ingestion [28% in Cohort 1 vs 7.5% of Cohort 2, Chi sq 22.82, p<0.001]. Clinically, a Glasgow Coma Score of >10/15 comprised about 70% of Cohort 1, but only 28% of Cohort 2[Chi sq 58.18, p<0.001]. Secondly, shock [systolic BP<90mmHg] was prominent in Cohort 1[63%] as compared to Cohort 2[33%], Chi sq 50.926, p<0.001. The Odds Ratio for a fatal outcome in a patient with refractory shock was 6.07, p<0.001. The most significant ECG finding was QTc prolongation [Cohort 1(43%) vs Cohort 2(13%), p<0.001].Management factors revealed that atropinisation was inadequate in the majority of Cohort 1 patients [87%] and only 24% of Cohort 2 patients [Chi sq150.06, p<0.001].Ventilator support was long sustained in Cohort 1[73%] compared to Cohort 2[31%] Chi sq 109.47, p<0.001.
Conclusion: This study identified key factors like delayed presentation, alchohol co ingestion, GCS >10/15, refractory shock, QTc prolongation, need for prolonged ventilation and improper atropinisation influencing the outcome.
Relevance: The information gained from this study enabled us to locate and rectify the lacunae in the effective management of OP poisoned patients at our institute.

INTRODUCTION

Background

Organophosphate poisoning is a major global health concern. The mortality rate approximates 10-20%, in developing countries which take the brunt of the attack[1]. Organophosphates act by inhibiting Acetylcholinesterase at the neuromuscular junction, thereby flooding the Ach receptors with cholinergic transmission. The outcome is dictated by multiple factors like type and quantity of OP ingested, time to resuscitation, availability of expertise and infrastructure, Paroxynase 1 [PON1] status, and so on[2,3]. Though previous research studies had been informative on the subject, ambiguity exists over factors determining death or survival[4]. A comprehensive comparative study between the 2 ultimate outcomes [survival vs death] would help triage patients for effective management. In the resource constrained settings of tropical India a standard assessment protocol based upon clinical criteria is more than just required.

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In this study we aimed to identify the key factors which determine the outcome among OP poisoned patients. The clinical information so gathered would influence decision making and effective utilisation of intensive care facilities.

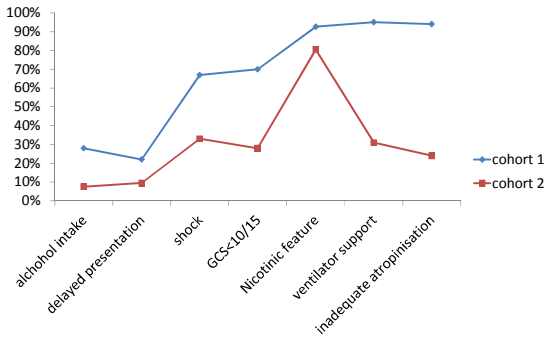
MATERIALS AND METHODS

This is a retrospective cohort study conducted at Government Villupuram Medical College and Hospital, Southern India. The comparison has been done among age matched OP poisoned patients [Cohort 1- Fatal outcome versus Cohort 2- Survived with/without morbidity]. 100 cases of Cohort 1 were compared with 200 cases of Cohort 2. Only moderate and severely poisoned patients were included in the study as per Peradeniya OP Scale[5].

Between April 2016 and March 2017, the case records of all patients who had been admitted for OP poisoning were scrutinised. 100 consecutive cases which ended in fatality were included into the study as Cohort 1 as per predefined criteria [Table 1]. Likewise, 200 patients who survived the toxicity with or without morbidity were included as Cohort 2. The data was collected under 3 heads- Pre-admission, [in hospital] Clinical features and Management factors. Pre admission factors like type of OP consumed, time to resuscitation, mode of first aid, etc were recorded. Various clinical parameters like pulse, blood pressure, respiratory rate, Glasgow Coma Scale, muscarinic, central and nicotinic manifestations of the poison were documented and computed. The treatment related information like dosage of atropine, mode of atropinisation and need for ventilatorysupportwere compared between the 2 groups. The software programme used was IBM SPSS version 20.

RESULTS

Though the choice was wide, Monochrotophos [12.5%], Profenophos[5%] and Chlorpyrifos[4%] were the preferred OP compounds by suicide intenders. In 72% of cases the compound could not be identified. Pre admission factors which had a significant bearing on the outcome were delayed presentation [>2 hours since exposure, 22 % of Cohort 1 vs 9.5% of Cohort 2, Chi sq 22.24,p <0.001] and alchohol co ingestion which was significantly high in Cohort 1 , 28 % vs 7.5% of Cohort, Chi sq 22.82, p<0.001. The 2 cohorts did not differ statistically much with regards to the nature of initial resuscitation [primary, secondary or tertiary care, type of decontamination] or the type of OP compound ingested.



Significant differences were found with regards to clinical features in both the Cohorts. Firstly, patients with Glasgow Coma Score of >10/15 comprised about 70% of Cohort 1, whereas they made up only 28% of Cohort 2[Chi sq 58.18, p<0.001]. Secondly, shock [systolic BP<90mmHg] was an early and prominent feature in Cohort 1[63%] as compared to Cohort 2[33%], Chi sq 50.93, p<0.001. The Odds Ratio for a fatal outcome in a patient with refractory shock in was 6.47*, CI 95%. Further, nicotinic manifestations [Resp muscle fatigue [21 %], fasciculations [23%], tachycardia [93%] were relatively common in Cohort 1. In Cohort 2 nicotinic manifestations occurred, albeit at a lesser frequency [Respiratory muscle fatigue 13%, fasciculations 17% and tachycardia 87%]. However these differences were not statistically significant. Central manifestations like seizures were also more frequent in Cohort 1[42%], though not statistically significant. Clinically, intermediate syndrome was recognised in 15% of Cohort 1 and 13.5% of Cohort 2 patients. Investigation related data revealed that sinus tachycardia [Cohort 1 (68%) vs Cohort 2 (57%)] was the most frequent ECG finding apart from QTc prolongation [Cohort 1(43%) vs Cohort 2(13%), p<0.001] and ST-T changes [Cohort 1(36%) vs Cohort 2 (21%)]. Respiratory failure was the cause of mortality in 85% of cases. About 62% of deaths occurred within 72 hours of consumption and among the late deaths 11% were due to complications of long term ventilation and ICU stay.

Management factors retrieved, revealed that atropinisation was inadequate in the majority of Cohort 1 patients [87%] whereas it was only 24% of Cohort 2 patients [Chi sq106.91, p<0.0001]. The atropine administration was not protocol based or goal directed and in most patients the end points were not reached. In Cohort 2 though the end points of atropinisation were achieved, but there was no evidence based method of administration, frequent bolus doses of atropine were practised. The incidence of respiratory failure did not differ much in the 2 cohorts [95% vs 87%], however the need for ventilatory support was long sustained in Cohort 1[73%] as compared to Cohort 2[31%]Chi sq 109.47, p<0.001. The administration of Oximes did not have any significant bearing on the outcome in both the cohorts.

Table.1 Patient selection criteria.

Inclusion criteria. • OP Poison exposed adult patients within 24 hours of intake. • As per POP scale, moderate and severe poisoned patients only.
Exclusion criteria. • Patients with major comorbid illnesses like heart failure, CRF. • Consumption of mixed poisons including organophosphate.

DISCUSSION

Organophosphates are lead killers. They are a heterogenous group with highly variable chemistry and clinical profile. Inhibition of Acetylcholinesterase at the neuromuscular junction leads to overstimulation of cholinergic receptors, ultimately culminating in death. Easy availability and high toxicity favour OP's as the preferred suicidal agents by

agricultural workers. Paucity of literature and lack of a standard management protocol compound the resuscitation of OP poisoned patients. Given this scenario, we endeavoured to compare matched cohorts ending with the 2 ultimate outcomes [survival and death] to enhance our understanding about the key mortality determinants.

The favoured compounds for poisoning were Monochrotophos, Profenophos and Chlorpyyrifos. Upon community introspection, it came to light that these agents were relatively inexpensive and had wide availability among pesticide sellers. In 72 % of cases the type of OP compound could not be ascertained and reliance was on the clinical picture to guide therapy.

these patients present in a moribund status and importance is accorded to stabilise them early with atropine first and later gastric lavage.

There are a lot of variations among the OP compounds with respect to their clinical presentation. For example in a study by Eddleston et al it was shown that Dimethoate poisoning is frequently associated with early coma[8]. In our study we considered the OP compounds as a single entity resulting in death or survival. The clinical picture predicting mortality was dominated by shock [Cohort 1[63%] vs Cohort 2[33%], Chi sq 50.93, p<0.001] and GCS >10/15[Cohort 1, 70% vs Cohort 2, 28%: Chi sq 58.18,p<0.001].

Table 2 Clinical features of OP poisoning in cohort 1 & 2

Pre Admission Data			
• Type of OP:			
Monochrotophos	12%	13.5%	
Profenophos	6%	4.5%	
Chlorpyrifos	4%	4%	
Unknown compound	69%	73.5%	
• Alchohol intake			Chi sq 22.82, p<0.001
• Delayed presentation	28%	7.5%	Chi sq 22.24, p<0.001
• Resuscitation centre:	22%	9.5%	
Primary care hospital			
Secondary care hospital			
Tertiary care hospital	17%	13%	
• Gastric lavage	72%	78%	
• Activated charcoal	11%	9%	
	71%	82%	
	21%	18.5%	
Clinical Features			
• Shock	67%	33%	Chi sq 50.93,p<0.001
• GCS <10/15	70%	28%	Chi sq 58.18,p<0.001
• Respiratory failure	95%	87%	
• Nicotinic features			
Muscle fatigue			
Fasciculation	21%	13%	
Tachycardia	23%	17%	
• CNS	93%	87%	
Seizure			
Delirium	42%	35%	
• Intermediate Syndrome	29%	21.5%	
	15%	13.5%	
Electrocardiogram			
• Tachycardia	68%	57%	
• QTc prolongation	43%	13%	Chi sq 59.64,p<0.001
• ST-T changes	36%	21%	
Management Aspects			
• Ventilator support	73%	31%	Chi sq 109.47,p<0.001
• Inadequate atropinisation	87%	24%	Chi sq 106.91,p<0.001

The quantity of poison consumed could never be ascertained in both the groups. Alchohol consumption was very common among patients in Cohort 1 [28%] as against 7.5% in Cohort 2. A plausible hypothesis is that the disinhibitory effect of alchohol on the central nervous system resulted in high risk behaviour among self poisoned patients. These intoxicated patients likely consumed more quantity of poison than their sober counterparts.

There were plenty of issues responsible for delay in presentation. Prime among them were delayed identification by care givers, transport related factors and mismatched health care infrastructure. Delayed presentation [>2 hours since exposure] made up 22 % of Cohort 1 vs 9.5% of Cohort 2, [Chi sq 22.24, p <0.001]. Most OP compounds are rapidly absorbed by the gastrointestinal route and timely resuscitation by gastric lavage and decontamination strategies have substantial influence on the outcome[6]. Furthermore many of

patient presenting with shock or coma was 2.09 and 5.60, CI 95%. In a retrospective study of OP poisoning, muscarinic symptoms and signs were the most frequent (84%) followed by CNS (78%) and nicotinic (17%)[8]. Approximately similar statistics were reflected in our study group which exhibited a muscarinic to nicotinic ratio of 92% to 18.5%. There was not much of selection bias, since only moderate and severely poisoned cases were included in the study group as per POP scale[5]. The most common cause of death in OP poisoning is respiratory failure. In large cohorts, respiratory failure is reported to occur in 24-66% of patients[9,10]. Severity of poisoning was the primary determinant of respiratory failure[11]. In our study we found that respiratory failure contributed to 85% of deaths, whereas hypoxic brain injury killed 10% of Cohort 1. A small minority [5%] was due to the effects of long term ventilation and could not be attributed to OP poisoning per se.

Common electrocardiographic findings which have been documented in previous research publications were QTc prolongation, ST-T segment changes and T wave abnormalities[12,13]. Other cardiac manifestations include sinus bradycardia or tachycardia, hypotension or hypertension, supraventricular and ventricular arrhythmias and ventricular premature complexes and noncardiogenic pulmonary edema[14]. In our study we observed that sinus tachycardia was the most common ECG change [68% Cohort 1 vs 57% Cohort 2]. Other features of prominence were ST-T changes [36% of Cohort 1 vs 21% of Cohort 2] and QTc prolongation [43% of Cohort 1 vs 13 % of Cohort 2: $p<0.001$].

There were a few management related facts which could not be ignored in the light of recent evidence on the subject. Management was complicated by the paucity of clinical trial based evidence to guide treatment, with no clear evidence for benefit from any therapy other than oxygen, atropine, and diazepam[15]. Previous research on the area proves that current treatment is only partly effective, with case fatality often greater than 10% in even the best intensive care units[16]. Most importantly, failure to identify particular insecticides and develop specific management protocols for each of this heterogenous group is the major stumbling block in treating these patients.

Akin to previous studies we found that Pralidoxime use did not have any beneficial effect on the mortality, given the fact that the individual compound has not been taken into account[17,18,19]. Detailed research performed earlier has proven that the Oximes are more efficacious in poisoning by Diethyl compounds and are not much effective for Dimethyl OPC's[7]. Though the incidence of respiratory failure didn't differ much between the 2 Cohorts the need for prolonged ventilatory support was higher among Cohort 1 [95%] patients than Cohort 2 [31%]. This may perhaps be attributed to the nature and quantity of the compound ingested which resulted in prolonged respiratory muscles paralysis.

Atropinisation was observed to be grossly inadequate in Cohort 1 as compared to Cohort 2 [87% vs 24%]. Literature search on the matter revealed that the administration of atropine should be protocol based [19,20]. The practice of giving huge bolus doses of atropine does not enjoy scientific support and proves to be harmful [21]. The regimen presently recommended is DDEF [Double Dose Every Five Minutes], wherein the dose of atropine is escalated at 5 minute intervals till complete atropinisation[19]. The end points for atropine administration include- dry tongue, dry mucosa, dry axilla, clear lung fields on auscultation, dilated pupils and normotension. One of the major contributors to mortality in this study was improper atropinisation not titrated by clinical end points. The need for prolonged ventilator support was another important factor determining mortality.

Limitations

The study was confounded by few factors like the particular type of OP poison consumed, which could be ascertained only in 28 % of cases. OP compounds were included as a single group, whereas there are lots of variations among the different compounds in terms of their toxicity profiles. Secondly, the exact quantity of consumption could never be ascertained for obvious reasons. Thirdly, the study was not powered enough to investigate endogenous factors determining outcome like Paroxanase 1 activity. Fourthly, a few of the late deaths [>72 hours] were not directly due to OP poisoning but were likely attributed to the complications of ventilation, ICU care, sepsis, etc. Well designed, multicentricrandomised controlled trials would be the solution for the unresolved questions shadowing the mortality determinants.

CONCLUSION

OP poisoning claims lives at disproportionately high rates compared to other xenobiotics. This study was instrumental in identifying certain key factors influencing the outcome. Most notably, delayed presentation, alchohol co ingestion, GCS >10/15, refractory shock, need for prolonged ventilation and improper atropinisation were associated with frequent fatalities. The information gained from the conduct of this study enabled us to locate and rectify the lacunae in the effective management of OP poisoned patients at our institute. The results also would help in salvaging similar situation in the vast majority of secondary and tertiary care institutions of rural tropics. Early resuscitation and evidence based management of these patients would certainly turn the tide against the grim outlook they face.

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