

Glycemic Status at the Time of Presentation in Acute Organophosphorous Poisoning and its Correlation with Severity and Clinical Outcome

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Abstract

Background: Organophosphorus insecticides (OPI) are one of the most extensively used classes of insecticides.

Huge scientific body of evidence suggests that OPI exposure is a major toxicological threat that may affect human and animal health because of their various toxicities such as neurotoxicity, endocrine toxicity, immunotoxicity, reproductive toxicity, genotoxicity and ability to induce organ damage, alterations in cellular oxidative balance and disrupt glucose homeostasis.

Mortality among organophosphorous (OP) poisoning patients despite advancements in its management is of concern. Of the various contributing factors, extremes and fluctuation in the glycemic status is a well documented parameter affecting the outcomes in critical illness although studies with respect to OP poisoning are deficient. All varieties of glycemic changes from hypoglycemia to hyperglycemia and ketoacidosis in OP poisoning along with other toxicological effects are reported, studies corroborating these findings are only few. The present endeavor was undertaken to study various glycemic changes in acute OP poisoning and its bearing on clinical severity and clinical outcome.

Aims and Objectives

1. To assess the glycemic status by estimating random blood glucose level at the time of admission in cases of acute organophosphorous poisoning

Introduction

Organophosphorous (OP) poisoning is a major health problem all over the world, particularly in a predominantly agrarian country like India. National crime bureau of India shows suicide by consumption of pesticides account for cases of suicidal poisoning per year. OPI exposure is a toxicological threat that may affect human and animal health because of their various toxicities such as neurotoxicity, endocrine toxicity, immunotoxicity, reproductive toxicity, genotoxicity and ability to induce organ damage, alterations in cellular oxidative balance and disrupt glucose homeostasis.

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- To assess severity of the poisoning with various poisoning scales (PSS and POP) and level of serum pseudocholinesterase.
- To correlate the documented blood glucose level with the severity and clinical outcome.

Method: A prospective analytical study of 100 patients with diagnosed acute poisoning, above the age of 18 years, non diabetic, with no history of mixed poisoning or condition affecting blood glucose levels and fulfilling the inclusion and exclusion criterias was done over a period of one year. The glycemic status at the time of presentation was documented and the patients were grouped into hypoglycemics, euglycemics and hyperglycemics and the same was correlated with the severity and clinical outcome using descriptive statistics, association and test of significance using MedCalc.

Results: A prospective analytical study of 100 patients of acute organophosphate poisoning was done and on the basis of blood glucose levels at the time of presentation were further categorised into hypoglycemics (37%), euglycemics (52%) hyperglycaemic (11%). The outcome in terms of mortality was 59.45%, 9.6% and 63.63% in the respective groups. The ventilator requirements among the three groups were 94.59%, 53.84% and 100% respectively.

Chisquare test to study the association between the presentation Random Blood Glucose (RBG) and the established Peradeniya Organophosphorous Poisoning Scale (POP) (Table 1) and Poisoning Severity Scale (PSS) (Table 2) revealed the study to be statistically significant (p value= 0.001) indicating both the extremes of glycemic status are associated with higher clinical severity and poorer outcomes.

Conclusion: We conclude that the glycemic status at the time of presentation in acute organophosphate poisoning patients is a simple, cheap, reliable marker in guiding the clinical severity and outcome when considered with clinical severity scores and S.ChE in a resource limited country like India.

The results of various studies in critically ill patients have shown that stress-induced hyperglycaemia as well as hypoglycemia are strong predictors of increased mortality and adverse clinical outcome.^{1,3}

Extremes in glycemic status is found to be associated with increased risk of infectious complications and septic shock, reduced immune response, dehydration and electrolyte imbalances and lethal multiple organ failure in traumatic and acute ischaemic events.^{4,5}

Although poisoning is one of the important causes of significant morbidity and mortality, and appropriate management is very important in critically ill poison patients,⁶ acute poisoning induced hyperglycaemia and hypoglycemia has not been previously studied in these patients

The rising mortality despite adequate poisoning management forces us to investigate for other possible contributory factors. The glycemic status is one such variable that affects the outcome in critical illness

Thus, this study was done to assess the Glycemic status at the time of presentation in acute organophosphorous poisoning and its correlation with clinical severity and outcome.

Material and Methods

Material

Source of data

Data was collected from patients fulfilling the inclusion and exclusion criteria Admitted to the S.S.G. Hospital, Vadodara. Informed written consent was obtained from patient or a responsible attendant before including the patient in the study. In addition to Baroda city, a large cross section of population comes to SSGH from Central and North Gujarat as well as from the states of Rajasthan, Madhya Pradesh and Maharashtra.

Study design: Prospective Analytical study

Sample size: According to data obtained from previous studies and considering the local current rates of admission with organophosphorous

Table 1: Peradeniya organophosphorus poisoning scale (POP scale)

Parameters	Criteria	Score
Pupil size	≥2 mm	0
	<2 mm	1
	Pinpoint	2
Respiratory rate	<20/min	0
	≥20/min	1
	≥20/min with central cyanosis	2
Heart rate	>60/min	0
	41-60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized/continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal commands	1
	No response to verbal commands	2
Seizures	Absent	0
	Present	1

Note: 0-3, mild poisoning; 4-7, moderate poisoning; 8-11, severe poisoning

Table 2: Poisoning severity scale

System	0	1	2	3
Gastrointestinal system				
Respiratory system				
Nervous system				
CVS				
Metabolic derangement				
Liver				
Kidney				
Blood				
Muscular system				
Skin / Local				
Eye				

poisoning in our hospital the sample size of 96 patients rounded off to 100 has been considered. (Ref. Medcalc software)

Data collection: 1 year period-Nov 2016 to Nov 2017

Patients fulfilling following inclusion and exclusion criteria were enrolled for the study.

Inclusion criteria

- Patients or the relatives who have given informed written consent.
- Patients who are above 18 years of age.
- Patient with alleged history of organophosphorous poisoning (ingestion / inhalational / contact) and diagnosed to have organophosphorous poisoning.

Exclusion Criteria

- Patients with age less than 18 years.

Table 3: POP score at presentation - Severity and its relation to ventilator support requirement and mortality

POP	No. of patients	Ventilator support	Expired
0 to 3 (Mild)	53	27	9
4 to 7 (Moderate)	47	47	25
8 to 11 (Severe)	0	0	0
Total	100	74	34

Table 4: PSS score - severity and its relation to ventilator support requirement and mortality

PSS	No. of patients	Ventilator support	Expired
0 to 3 (Mild)	25	2	0
4 to 7 (Moderate)	57	54	20
8 to 11 (Severe)	18	18	14
Total	100	74	34

2. Patients with history Diabetes Mellitus.
3. Patients already treated at other centres and referred to our centre for further management with no details available at the time of first presentation.
4. Patients who had consumed alcohol, drugs, mixed poisoning that could affect the glycemic status of the patients.

Methods

Patients

The prospective analytical study was done in SSG Hospital, Vadodra. Patients aged over 18 years with a diagnosis of acute organophosphorous poisoning were included in the study. The diagnosis was based on history of short term exposure or contact, characteristic clinical signs and symptoms, decrease in serum cholinesterase activity. Subjects wherein the exact nature of the poisoning could not be established and known diabetics were excluded from the study.

A detailed history including particulars regarding age sex, type of compound consumed, time-lag between consumption and initiation of treatment was taken followed by a thorough clinical examination. The severity of the poisoning was graded by POP scaling and PSS.

Severity of Poisoning: Mild (score 0-3), Moderate (score 4-7), Severe (score 8-11)

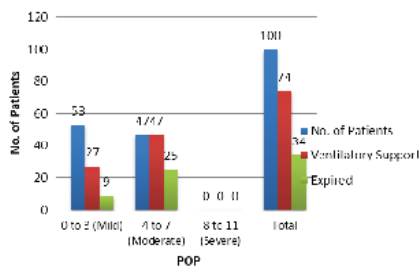


Fig. 1: POP score at presentation - Severity and its relation to ventilator support requirement and mortality

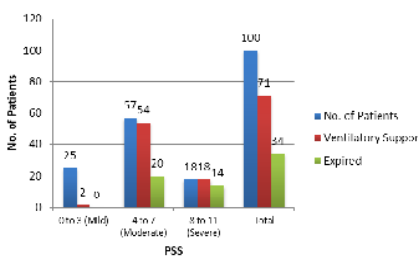


Fig. 2: PSS score - severity and its relation to ventilator support requirement and mortality

Hyperglycemia and hypoglycemia were defined as random blood glucose of more than 200 mg/dL and hypoglycemia as less than 80 mg/dL. Glycosuria was detected using ketodiastix strips.

The presence of hyperglycemia or glycosuria or hypoglycemia or ketosis was correlated with the severity of the poisoning with respect to the nature of the compound consumed, the time lag between consumption and initial treatment, the clinical grade of poisoning, the serum pseudocholinesterase level and the requirement of assisted ventilation and outcome.

Following investigations were carried out in each patient.

Investigations

1. Random blood glucose level at the time of admission.
2. Pseudocholinesterase levels at the time of admission.
3. Complete blood count.
4. Liver function tests.
5. Serum creatinine and blood urea.
6. Urine analysis.
7. HbA1C. (if hyperglycemia documented)
8. ECG.

Other relevant investigations if required.

Table 5: Glycemic status (RBG) at presentation - severity and its relation to ventilator support requirement and mortality

RBG	Ventilator support	Expired
<55-80 (Hypo) (n=37)	35	22
101 to 200 (Normo) (n=52)	28	5
>200 (Hyper) (n=11)	11	7
Total (n=100)	74	34

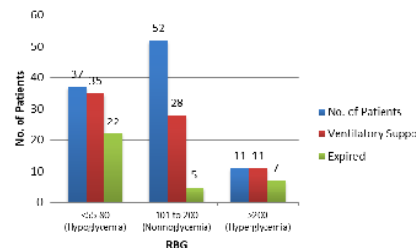


Fig. 3: Glycemic Status (RBG) at presentation - Severity and its relation to ventilator support requirement and mortality

Definitions

Hyperglycemia and hypoglycemia are defined as random blood glucose of more than 200 mg/dL and hypoglycemia as <55 mg/dL (severe) 56-70 mg/dL (moderate) and 71-100mg/dL (mild).

Acute renal failure was diagnosed if the serum creatinine level increased to >1.27 mg/dL in men or 1.03 mg/dL in women.

Acute respiratory failure was defined as respiratory insufficiency requiring intubation and mechanical ventilation for more than 24 hours, regardless of the fraction of inspired oxygen (Indications for mechanical ventilatory support were pulmonary secretions with hypoxia and respiratory depression ie RR more than 30, spO2 less than 90%, respiratory failure and altered sensorium.)

Hypotension was defined as systolic blood pressure less than 90mmHg.

HbA1c if >7, pt was considered diabetic and was excluded from the study.

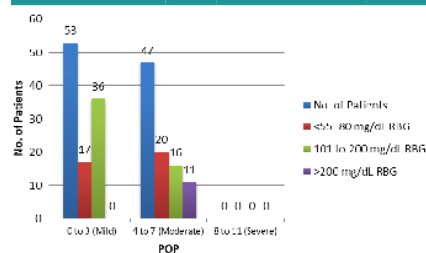
For the study purpose, on the basis of on presentation Random blood glucose (RBG) levels, patients were grouped into three categories- hypoglycemics (RBG<80mg/dL), euglycemics (101-200mg/dL) and hyperglycemics (>200mg/dL)

Data analysis

The mortality and ventilator requirement in each group were compared with another in terms of

Table 6: Association of glycemic status (RBG) of patients with different grades of POP score

POP	N	<55-80 mg/dL	101 to 200 mg/dL	>200 mg/dL
0 to 3 (Mild)	53	17	36	0
4 to 7 (Moderate)	47	20	16	11
8 to 11 (Severe)	0	0	0	0
Total	100	37	52	11

**Fig. 4: Association of glycemic status of patients with different grades of POP score**

descriptive analysis and chi square test was applied to look for the statistically significant association between the glycemic status and the clinical scores like POP and PSS using MedCalc

Results

The demographic and clinical characteristics of 100 patients revealed a male preponderance (63%) and females (37%). The mean age of the study population was 25.5±8 (range 18-65 yrs). The overall incidence was higher in married group and the most common cause of poisoning was suicidal (83%) followed by accidental (16%) and unknown (1%). Ingestion (88%) was the most common mode of poisoning followed by inhalational (12%).

The population in grade 1 and grade 2 POP scores were 53% and 47% respectively. The percentage of population in grade 1,2,3 of PSS were 25%, 57% and 18% respectively.

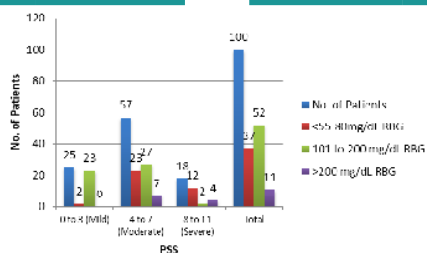
Out of 100, 74% patients developed respiratory failure necessitating ventilator requirement. The overall mortality was 34% and 66% patients were discharged.

The ventilator requirement and mortality was higher with higher grades of and POP (Table 3 and Figure 1) and PSS (Table 4 and Figure 2)

As per on presentation RBG, 37% had hypoglycemia, 52% were euglycemic and 11% were hyperglycemics. The ventilator requirement in the three groups were 94.59%, 53.84% and 100% respectively and the mortality was 59.45%, 9.6% and 63.63% respectively (Table 5 and Figure 3). Hence a very

Table 7: Association of glycemic status (RBG) of patients with different grades of PSS

PSS	N	<55-80mg/dL	101 to 200 mg/dL	>200 mg/dL
0 to 3 (Mild)	25	2	23	0
4 to 7 (Moderate)	57	23	27	7
8 to 11 (Severe)	18	12	2	4
Total	100	37	52	11

**Fig. 5: Association of glycemic status of patients with different grades of PSS**

strong correlation between the glycemic status, ventilator requirements and mortality was established.

Further, the RBG was compared with POP and PSS to look for statistically significant association between the extremes of glycemic status and higher grades of these clinical severity scores using Chi-square test in MedCalc. The results were statistically significant ($p=0.0001$, $\text{Chisquare}=18.643$, $\text{DF}=2$ for POP and $p=0.0001$, $\text{Chisquare}=28.748$, $\text{DF}=4$ for PSS) (Tables 6, 7 and Figures 4, 5).

The association between extremes of glycemic status and the grades of POP is statistically significant ($P<0.0001$, Chi Square 18.643, $\text{DF}=2$).

The association between extremes of glycemic status and the grades of PSS is statistically significant ($P<0.0001$, Chi Square 28.748, $\text{DF}=4$)

Discussion

Among 100 patients studied, the poisoning was more common among males, age group of 18-40 years and married cohort. The most common cause was suicidal and the most common mode was ingestion. The mean time lag between the consumption and medical attention seeking was 5±2.6 hrs.

Vomiting, abdominal pain, altered sensorium and breathlessness were the most common symptoms. In emergency department, most patients had POP grade 1 and on further follow up in critical care unit, the majority developed grade 2 and 3 PSS. Respiratory failure necessitating the need for ventilator was the most lethal and most common

complication.

Of the study group, the glycemic status on presentation was in the following order of decreasing frequency-euglycemia (52%) followed by hypoglycaemia (37%) and hyperglycemia (11%) whereas the study by *Ali Mohammad Sabzghabee et al.*⁷ showed 62%, 14% and 23% respectively (hyperglycemics more than hypoglycemics).

Our study showed that the severity of poisoning was of grade 2 or more in both the extremes of glycemic status (100% in hyperglycemia and 90% in hypoglycaemia) and majority of the euglycemics had grade 1 poisoning which is in correlation with study by *Ali Mohammad Sabzghabee et al.*⁷

The ventilator requirements and complications were 94.59%, 53.84% and 100% among hypoglycemics, euglycemics and hyperglycemics respectively. The study by *Preeti G Pendkar et al.*⁸ showed the incidence of complications to be 73% in hyperglycemics, 27% in normoglycemics and hypoglycemics were not included in the study.

The mortality in *Ali Mohammad Sabzghabee et al.*⁷ was 10.4%, 3.71% and 15% in hypoglycemics, euglycemics and hyperglycemics whereas the overall mortality was higher in our study but keeping in trend with the previous study in the order of decreasing frequency-hyperglycemia (63.63%), hypoglycemia (59.45%) and normoglycemia (9.6%).

Understanding the mechanism of glycemic variability in OP poisoning and its burden on the clinical outcomes are of importance as our study shows a significant association between the extremes of the the glycemic status and complications and outcome

Although the studies enlightening the mechanistics of glycemic variability in acute OP poisoning are few, the following plausible reasons could be attributed.⁹⁻¹²

1. The effect of stress hormones,
2. Overproduction of

proinflammatory cytokines,

3. Pancreatic insufficiency,
4. Altered hepatic metabolism due to depletion of enzymes by the toxin that play major role in glucose metabolism and
5. The prior nutritional status of the patient.

Hyperglycemia and fluctuation in the glycemic status are known to be deleterious in critical illness as they increase the overall complications, morbidity, hospital stay and mortality.¹³⁻¹⁵

A strong association with hyperglycemia and critical illness neuropathy is documented that contributes to increased need and duration of mechanical ventilator support and other complications and mortality.

Likewise, hypoglycemia is an independent marker of severity and mortality in critical illnesses. The five cause death categories in patients with critical illness and hypoglycemia are¹⁶

1. Neurologic
2. Cardiovascular
3. Hypoxic respiratory failure
4. Liver related and
5. Others.

Individual hypoglycemic episodes are associated with biologic toxicity by increasing the systemic inflammatory response, inducing neuroglycopenia, inhibition of corticosteroid stress response and cerebral vasodilation.

Hence we urge that the management of both the extremes of glycemic status and the fluctuation is of prime importance in acute OP poisoning like any other critical illness for better outcomes.

The management protocol for stress

hyperglycemia¹⁴ as per ADA 2012 is by targeting a goal of 130-180 mg/dL. The dose of the intravenous insulin administration as per the RBG is as following:

140-179mg/dL - Start I.V infusion at 1IU/hr

180-199mg/dL - Start I.V infusion at 2IU/hr

200-249mg/dL - Bolus 2IU iv insulin followed by infusion at 2IU/hr

250-299mg/dL - Bolus 4IU iv insulin followed by infusion at 2IU/hr

>300mg/dL - Bolus 4IU iv insulin followed by infusion at 4IU/hr.

Management of hypoglycemia requires continuous glucose monitoring, identification of symptoms, treating the precipitants and prompt administration of intravenous dextrose.

Conclusion

We conclude that the extremes of glycemic status at presentation in acute Organophosphate poisoning is strongly associated with the severity, complications and the mortality hence can be used as a cheap, simple, reliable marker of prognosis along with the s. chE, and other clinical scores like POP and PSS in a resource limited country like India.

However the studies to understand the Organophosphate induced glycemic variability and its bearing on the severity and outcomes are very few. Prospective studies regarding the same in a large cohort are desirable with focus on mechanistic association between the glycemic status and outcomes. Also the importance of continuous glucose monitoring and the management of the fluctuations in critical care settings needs to be investigated and emphasized.

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