

Original Research

Glycemic status at the presentation and its role as marker of severity and outcome in patients with organophosphorus poisoning

Mohammad Hayat Bhat¹, Sajad Qadir Bhat², Ishrat Hussain Dar², Javaid Ahmad Bhat^{1,*}

¹ Department of Endocrinology, Superspeciality Hospital, Government Medical College, Srinagar, Kashmir, India

² Department of Medicine, Government Medical College, Srinagar, Kashmir, India

*Correspondence to: Javaid Ahmad Bhat, Department of Endocrinology, Superspeciality Hospital, Government Medical College Srinagar, India, E-mail: javaidrasool711@gmail.com

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Abstract

Background and aims: There has been an increasing recognition of the various metabolic abnormalities in patients with acute organophosphorus (OP) poisoning including disturbed glucose homeostasis. We assessed the glycemic status at the presentation and its role as a marker of severity and clinical outcome in patients admitted with acute OP poisoning. **Material and method:** This was a prospective observational study, involving 400 patients above 18 years of age admitted to the emergency department of a tertiary care institution in Northern India. The biochemical parameters including random plasma glucose, serum cholinesterase, severity and outcome were determined. Patients were grouped according to their admission plasma glucose into hypoglycemic (<70 mg/dl), euglycemic (RBS=70–199 mg/dl) and hyperglycemia (RBS≥200 mg/dl) groups. **Results** The hyperglycemia, hypoglycemic and normoglycemia (RBS=70–199 mg/dl) at admission was present in 29.5%, 14.5% and 56% of patients. Five patients (4.24%) among hyperglycemia presented with diabetic ketoacidosis (DKA). Extremes of glycemic status including hyperglycemia and hypoglycemic were significantly associated with prolonged hospital stay (>7 days), need for mechanical ventilation and mortality in 66% and 60%, 68% and 69%, 35% and 33%, respectively compared to 18%, 24% and 4% in normoglycemic group, respectively. Overall mortality in our study cohort was 17%. Furthermore, extremes of glycemic status at presentation were significantly associated with the clinical severity, depression in serum cholinesterase levels, add need for ICU care. **Conclusions:** Glycemic extremes including both hyperglycemia and hypoglycemic are common in patients with acute OP poisoning and are significantly associated with morbidity and mortality. It can be used as a simple and reliable predictive marker to identify patients in need of intensive monitoring and admission to the intensive care unit (ICU).

Keywords: organophosphorus poisoning, glycemic status, hyperglycemia, hypoglycemic.

Background and aims

The increasing health hazards resulting from human exposure to the agro pesticide, especially to organophosphorus (OP) compounds especially from agricultural areas of developing countries and grim outcome associated with poisoning despite the advances in basic healthcare and various modalities of management has been a growing concern. The problem is further accentuated in our country due to the easy availability of these compounds over the counter, and their

indiscriminate usage in the face of limited availability of health care facilities particularly the ICU care contributing further to the increased burden of morbidity and mortality seen in these patients.

Organophosphate compounds are agricultural insecticides that act by inhibiting acetylcholinesterase enzyme which is responsible for the degradation of acetylcholine. This inhibition makes acetylcholinesterase enzymatically inert resulting in increased concentration of acetylcholine leading to overactivity of muscarinic and



nicotinic receptors in the myoneural junction in addition to excess cholinergic effects in the central nervous system, and peripheral nervous system. Enhanced lipid peroxidation and low glutathione level seen in patients with OP poisoning are associated with damage to cell membrane and DNA, resulting in cell death indicative of oxidative stress and thus adverse effects on different systems in the body (1).

In recent years, there has been increasing recognition of metabolic abnormalities other than choline esterase inhibition, in patients with OP poisoning including disturbed glucose homeostasis plays a key role in determining the final outcome. A variety of glycemic changes ranging from hypoglycemic to hyperglycemia and rarely ketoacidosis in Organophosphate poisoning are reported (2) The impact of metabolic abnormalities on the severity parameters and clinical outcome has prompted the clinicians to find the different clinical and/or laboratory parameters at initial assessment to be used as markers of severity to triage the OP poisoning patients to the necessity for various modalities of treatment including ventilatory support and to assess the prognosis. Glasgow coma scale (GCS<13) acute physiology and Chronic Health Evaluation II (APACHE II) score >26, serum acetylcholinesterase level, creatinine phosphokinase, erythrocyte cholinesterase level, blood pH and total atropine dose have been propounded as predictive marker of severity including morbidity and mortality in a number of studies, however, contradictory results have limited their utility as a predictive marker of severity and prognosis.

Of late, there has been increasing recognition of the effects of OP compounds on glucose homeostasis and together with the fact that extremes or fluctuation in the glycemic status are known to be deleterious in critical illness for they tend to increase the overall complications including morbidity, hospital stay and mortality (3, 4) have rekindled the interest in exploring the impact of dysglycemia on the outcome of OP poisoning.

The present study was undertaken to study the glycemic changes in acute organophosphorus poisoning and its relationship with severity, morbidity, and mortality. This might enable

clinicians to identify patients in need of intensive monitoring and in decision making regarding need and admission to intensive care unit (ICU).

Material and method

After obtaining the ethical clearance from the Institutional Ethical Committee, the present study was conducted in the Postgraduate Department of Medicine, Government Medical College, Srinagar, Jammu and Kashmir, India.

Study design and patients

It was a prospective observational study involving 400 patients carried over a period of 2 years from October 2018 to October 2020. The study was performed in accordance with the Declaration of Helsinki statement for medical research involving human subjects.

Inclusion criteria

Patients aged 18 years or above admitted with an alleged history of organophosphorus poisoning (ingestion/inhalational/contact) and diagnosed to have organophosphorus poisoning were included in the study after obtaining well-informed written consent from the patients or their relatives.

Exclusion criteria

1. Patients aged less than 18 years and/or with a history of diabetes mellitus, chronic liver disease, chronic kidney disease or any other comorbidity that could affect the glycemic status of the patients.
2. Patients already treated at other centers and referred to our center for further management with no details available at the time of the first presentation.
3. Patients who had consumed alcohol, drugs, mixed poisoning that could affect the glycemic status of the patients.

The presumptive diagnosis of organophosphorus poisoning was based on history, circumstantial evidence and characteristic clinical features.

Blood samples for estimation of random plasma glucose and serum cholinesterase were collected at the time of admission and processed in a fully automated auto analyzer. Serum cholinesterase was estimated by using Beckman Coulter machine and analysis of the sample by spectrophotometry method (Normal range of serum acetylcholinesterase: 4–11 kU/L35). Random plasma glucose was determined by GOD-POD (glucose oxidase and peroxidase) method. Patients were grouped according to their admission plasma glucose into hypoglycemic (<70 mg/dl), euglycemic (RBS=70–199 mg/dl) and hyperglycemia (RBS≥200 mg/dl). Urine was tested for the presence of sugar and ketone bodies using a reagent strip for urine analysis.

The clinical severity of the acute organophosphorus poisoning was measured by using Peradeniya Organophosphorus Poisoning (POP SCALE) and patients were subsequently graded into mild, moderate and severe, based on Peradeniya organophosphorus poisoning (POP) scale.

Statistical analysis

The recorded data was compiled and entered in a Microsoft Excel spreadsheet and analyzed using Epi Info. Continuous variables were summarized as mean±SD and categorical variables were summarized as percentages. The Chi-square test was used to analyze the relationship between two categorical variables. One-Way ANOVA was used to analyze the difference between the 2 means. Pearson's correlation coefficient was used to analyze the relationship between two continuous variables. Landis and Koch guidelines were used to assess the correlation coefficient. Two-sided p-values were reported and a p-value<0.05 was considered statistically significant.

Results

A total of 400 consecutive patients admitted with OP poisoning were included in the study.

The study cohort comprised 72 males and 328 females in the ratio of 1:4.56. There was female preponderance in our study with 82% females and 18% males with the majority (88%) of them coming from rural areas compared to 12% (n=47) from urban areas. Ingestion was the main model used for self-poisoning by the patients in 99% (n=396/400) and only 1% (n=4) had inhalational exposure. Suicide was the most common motive seen in 93% of patients while in 7% (n=27) there was an accidental exposure to OP poison.

According to POP scale, 50% (n=200) patients had mild poisoning (POP Score 0–3), 35% (n=140) had moderate poisoning (POP Score 4–7) and 15% (n=60) patients had severe poisoning (POP Score 8–11). Serum cholinesterase level was >2 kU/l (mild poisoning) in 31% (n=125), 1–2 kU/l (moderate poisoning) in 46% (n=185) and <1 kU/l (severe poisoning) in 23% (n=90) patients.

Patients were grouped according to their admission plasma glucose into hypoglycemic (<70 mg/dl), euglycemic (RBS=70–199 mg/dl) and hyperglycemia (RBS≥200 mg/dl) groups (Table 1). The mean A_{1c} (95% CI) level of the study group at the time of admission was 5.12±3.44 gm% (4.63–5.61) with non-significant statistical differences between the groups. The mean random plasma glucose of the study population at the time of admission was 143±85 mg/dl with 29.5% (n=118) and 14.5% (n=58) patients having hyperglycemia and hypoglycemic respectively on the basis of admission random plasma glucose. About 56% of patients present in the study were having normal glycemia. Five patients (1.25%) presented with diabetic ketoacidosis (DKA). Glycosuria was present in 53.3% (n=213) patients out of which glycosuria along with hyperglycemia was seen in 39.4% (n=84) patients.

Hyperglycemia was found to have a statistically significant negative correlation with serum cholinesterase level; however, with hypoglycemic serum cholinesterase level was having a statistically significant positive correlation.

Clinical severity based on the POP score was having a statistically significant positive correlation with elevated admission plasma glucose levels and exhibited a statistically significant negative correlation with low admission plasma glucose levels and serum cholinesterase level. The

Table 1: Comparative analysis of the various initial parameters among patients categorised into different glycemic groups based on the admission random plasma glucose level.

Severity variables	Admission plasma glucose (mg/dl)			p-Value
	Normoglycemic group (RBS=70-199) (n=224)	Hypoglycemic group (RBS<70) (n=58)	Hyperglycemic group (RBS≥200) (n=118)	
Age (years)	31.6±12.8	35.0±14.1	36.7±14.7	0.003*
Sex (F:M)	188:36	48:10	92:26	0.389
RBS (mg/dl)	105±32	55±8	259±50	0.000*
HbA _{1c} (%)	4.88±0.28	4.76±0.30	5.33±4.37	0.579
Glycosuria	128 (57)	1 (2)	84 (71)	0.000*
Ketonuria	0	0	6 (5)	0.001*
POP score	2.18±1.95	5.52±1.95	5.88±1.94	0.000*
Peradeniya OP Poisoning (POP) Scale				
Mild (0-3)	190 (85)	04 (7)	06 (5)	0.000*
Moderate (4-7)	21 (9)	43 (74)	76 (64)	
Severe (8-11)	13 (6)	11 (19)	36 (31)	
Cholinesterase level (kU/l)				
<1 (n=90)	16 (7)	22 (38)	52 (44)	0.000*
1-2 (n=185)	101 (45)	29 (50)	55 (47)	
2-6 (n=125)	107 (48)	7 (12)	11 (9)	
Hospital stay				
<7 days	183 (82)	23 (40)	40 (34)	0.000*
≥7 days	41 (18)	35 (60)	78 (66)	
HDU requirement	61 (27.2)	46 (79.3)	102 (86.4)	0.000*
Intermediate syndrome	21 (9.4)	11 (19)	39 (33.1)	0.000*
Mechanical ventilation n (%)	53 (24)	40 (69)	80 (68)	0.000*
Mortality n (%)	9 (4)	19 (33)	41 (35)	0.000*

Categorical data are shown as %; continuous variables are shown as mean±standard deviation. *Significance. F: Females, M: Males, RBS: Random blood sugars, HDU: High dependency unit.

graded fall in serum cholinesterases seen with rising in POP score seen in our study indicated an increase in severity of poisoning.

Complications were seen in 84% (n=100/118) patients who had hyperglycemia and 83% (n=48/58) patients in hypoglycemic group compared to 20% (n=45/224) in patients of normoglycemia. Hyperglycemia and hypoglycemic were significantly (p=0.000) associated with prolonged hospital stay (>7 days) in 66% and 60% of patients compared to 18 % in patients with normoglycemia. High dependency unit care and the presence of intermediate syndrome were seen more in patients with glycemic extremes compared to normoglycemia (p=0.000).

Ventilator support was needed in 68% (n=80/118) patients having hyperglycemia, 69% (n=40/58) patients of hypoglycemic and 24%

(n=53/224) patients of normoglycemia. The need for ventilatory support was significantly more in patients with glycemic extremes compared to normoglycemic patients (p=0.000).

In our study, out of a total of 400 patients, 329 survived and 69 died which translates into an overall mortality of 17%. Mortality was highest in a dysglycemic group comprising of 35% (n=41/118) in patients with hyperglycemia, 33% (n=19/58) in the patients of hypoglycemic and 4% (n=9/224) in those with normal glycemia.

Discussion

Organophosphate poisoning continues to be the major cause of the accidental health

hazard and deliberate self-harm particularly in a predominantly agrarian country like India. Despite advancements in its management, acute OP poisoning continues to be a leading cause of mortality besides morbidity in recovered patients. Identification of parameters predictive of morbidity at presentation might help in decision-making in places of limited resources like rural settings in developing countries. Glycaemic variability is a well-documented parameter affecting the outcomes of these patients and has been found to be associated with increased risk of infectious complications, dehydration, reduced immune response, electrolyte imbalances and septic shock leading to multiple organ failure. Early identification of the poor prognostic indicators may help to predict the treatment outcome of acute organophosphate poisonings and may help in the timely intervention so as to bring down the complications and mortality.

The present study was undertaken to determine random plasma glucose level at presentation, a simple and inexpensive tool and its role as a predictive marker of severity and outcome in patients admitted with acute OP poisoning. A total of 44% of patients had deranged glycaemic status at the time of admission including 29.5% with hyperglycemia, 14.5% with hypoglycemic. Among the patients with hyperglycemia, 5 patients (4.24%) were found to have diabetic ketoacidosis. Our findings were consistent with results from earlier studies which documented the presence of glycaemic abnormalities including hyperglycemia, hypoglycemic and diabetic ketoacidosis in patients of OP poisoning (5-7).

Diabetic ketoacidosis (DKA) though rare, is a known complication in patients of acute OP poisoning and was present in five (1.25%) patients of this study. The presence of DKA in similar other studies involving OP poisoning patients highlights the importance of high suspicion of the condition to diagnose it early and manage this potentially life-threatening complication (8, 9). The glycosuria was present in significant number of patients in our study which is consistent with the findings in an earlier study where glycosuria alone was observed in 56% of cases with OP poisoning and in 20% of patients along with hyperglycemia (10). Oxidative stress at the renal tubular

level in addition to renal damage associated with metabolic changes secondary to the cholinergic effect of OP poisoning may be the most likely explanation for the presence of glycosuria in significant number of patients.

A number of mechanisms has been forwarded to explain the occurrence of hyperglycemia arising as a result of both acute and chronic exposure to OP poisons. Role of oxidative stress, inhibition of paroxanase, stimulation of adrenal glands and release of catecholamines, and effect on the metabolism of liver tryptophan are some of the proposed mechanisms to explain the derangement of glucose metabolism in OP poisoning (11).

The continuous cholinergic stimulation as a result of the accumulation of acetylcholine consequent to irreversible inhibition of cholinesterase enzyme by OP compounds results in catecholamine excess along with the enhanced release of ACTH from the anterior pituitary that translates into hyperglycemia. Similarly increased glycogenolysis and neoglucogenesis via activation of glucocorticoid and adrenergic receptors also contribute to the deranged glycaemic control (12, 13). Increased production of glucose as a result of induction of metabolic pathways in the brain and skeletal muscles also results in hyperglycemia. The role of insulin resistance and insulin secretory defect following OP exposure have also been proposed as a mechanism for the development of hyperglycemia in these patients (14). The 'unmasking' of the insulin secretory defect following insult though subacute to pancreatic Langerhans islets including diazinon-induced oxidative/nitrosative stress as a consequence of OP exposure is further proposed to result in dysglycemia. Also, damage to renal tubules seen in OP poisoning could also contribute to the pathogenesis of dysglycemia.

In the present study, it was observed that admission hyperglycemia and hypoglycemic were significantly associated with complications in 84% and 82% of the patients, respectively compared to only 20% (45/223) in the normoglycaemic group.

One of the observations of our study was that patients with extremes of glycaemia (hypoglycemic or hyperglycemia) at the presentation had

moderate to severe disease in the majority (95 and 93%, respectively) of them compared to 15% of the patients with normoglycemia who had rather a mild form of the disease in the majority (85%). This observation gives credence to the fact that patients of acute OP poisoning with dysglycemia suffer from higher grades of severity thus undermining the importance of knowing the status of glycemic status at the presentation and warrants due consideration in decision making regarding the need for close observation and admission to ICU. Furthermore, the presence of hyperglycemia at presentation had a significantly positive correlation with clinical severity of the disease ($\rho=0.3522$, $p=0.0001$); while a statistically significant negative correlation was found between hypoglycemic and clinical severity ($\rho=-0.4864$, $p=0.0001$). These findings are in agreement with the observations documented in the earlier studies (2, 5). Raveendra KR, et al. in his study found that severe poisoning (POP score 8–11) was seen in 30% of patients with hypoglycemic and 60% in the hyperglycemic group as compared to only 16% of euglycemic patients. Similarly, Raghapriya R et al. found that both hypoglycemic and hyperglycemia were associated with high POP severity scores.

In our study, severe suppression of serum cholinesterase (<1 kU/l) was seen in only 6% of normoglycemic patients compared to 44% and 40% in patients with hyperglycemia and hypoglycemic, respectively indicating greater suppression of cholinesterase was seen in the patients with OP poisoning with extremes of blood sugar. Furthermore, it was observed that serum cholinesterase level had a statistically significant negative correlation ($\rho=-0.3153$, $p=0.0005$), with high blood glucose levels and a significant positive correlation with low blood glucose level ($\rho=0.4172$, $p=0.0011$). Similar results were documented in the previous study where they found that severe suppression of serum cholinesterase was seen in 30% of hypoglycemic patients and 50% of hyperglycemic patients (5).

It was further observed that both hyperglycemia and hypoglycemic showed a significant ($p=0.001$) association with the need for ventilator

support. In our study, 68% and 69% of patients with hyperglycemia and hypoglycemic needed ventilator support compared to only 24% of normoglycemic patients. Similar observations were made in other studies involving OP poisoning patients. In one of the study, it was observed that of 94% patients with hypoglycemic, 100% with hyperglycemia and 53% with normoglycemia needed mechanical ventilation (2) in similar to the observation of 80% and 72% of patients with hyperglycemia requiring mechanical ventilation in other studies (5, 6).

Organophosphate poisoning is a serious clinical entity and the estimated mortality from OP ingestion ranges from 10% to 20% (15–17). In this study, the overall mortality was 17% which is comparable to results documented in earlier studies. Mortality was much higher in patients with hyperglycemia (35%) and hypoglycemic (33%) compared to those in the normoglycemia (4%) thus translating into the overall mortality of 17% which is comparable to results documented in earlier studies (2, 18, 19). The above results indicate glycemic status at admission is a good marker for predicting mortality in patients with OP poisoning.

Conclusions

Hyperglycemia as well as hypoglycemic are commonly observed in cases of organophosphorus poisoning and are commonly associated with moderate to severe poisoning. Extremes of glycemic status at presentation in acute organophosphorus poisoning are strongly associated with the clinical severity, depression in serum cholinesterase levels, complications, need for mechanical ventilation and mortality.

Admission random plasma glucose levels >200 mg/dl or <70 mg/dl can be used as inexpensive readily available and reliable markers of prognosis along with the serum cholinesterase level and clinical scores like Peradeniya OP Scale in a resource-limited country like India. Thus it may be helpful for the treating physician in careful monitoring and aggressive management of severe cases, thereby reducing mortality and saving crucial lives.

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