대한임상독성학회지 2015:13(2):55~61
Volume 13, Number 2, December, 2015

Journal of The Korean Society
of Clinical Toxicology

원 저

유기인계 중독환자에서 내원시 혈당과 예후와의 연관성

전남대학교 의과대학 응급의학교실

이성도 · 문정미 · 전병조

Initial Blood Glucose Can Predict the Outcome of OP Poisoning

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Purpose: Many studies have examined the mechanisms of impaired glucose homeostasis after organophosphate (OP) exposure, however no study has evaluated the clinical utility of blood glucose measurements in patients with OP poisoning. The current study was conducted to evaluate the initial glucose level at presentation and the glycemic variables during the first 3 days after admission as a predictor of mortality.

Methods: This retrospective observational case series included 228 patients with a history of OP poisoning. Among other clinical data, information on the initial glucose level at presentation and mean glucose level, delta glucose level, and the presence of a hypoglycemic event during the first 3 days of admission, was collected.

Results: Survivors had lower initial glucose levels at presentation and glucose variability during the first 3 days of admission compared to non-survivors. The frequency of hypoglycemic events was higher in non-survivors. In multivariate analysis, the initial glucose level (> 233 mg/dl) was an independent predictor of mortality, along with age.

Conclusion: The initial glucose level at presentation can be helpful in prediction of mortality in cases of OP intoxication at bedside. The physician should pay attention to patients with a glucose level >233 mg/dl at presentation after ingestion of OP.

Key Words: Organophosphates, Pesticide, Glucose, Outcome

Introduction

A number of studies have demonstrated the relationship between blood glucose levels and poor health outcomes[1-6]. The association of hyperglycemia at presentation with mortality has been reported in methanol and aluminum phosphide poisoning, as well as in acute myocardial infarction (AMI), ischemic stroke, and trauma[1-3]. Additionally, glucose variability (GV) has recently been shown to be associated with mortality in both non-critically ill and critically ill patients[4,5].

In animal studies, hyperglycemia has been observed following exposure to OPs, such as malathion, parathion, or chlorpyrifos[7-10]. While many studies have investigated the mechanisms of impaired glucose homeostasis after OP poisoning[11-13], no study has evaluated the clinical utility of blood

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투고일: 2015년 11월 2일 1차 심사일: 2015년 11월 21일
게재 승인일: 2015년 11월 26일

* 이 논문은 대한임상독성학회지 외 다른 학회지에 동시에 투고되지 않았으며 이전에 다른 학회지에 게재된 적이 없음을 선언합니다.

glucose levels in patients poisoned with OP.

The mortality from OP poisoning is as high as 20.0%, and approximately 86.4% of the patients with symptomatic OP intoxication require mechanical ventilation[14,15]. Considering the high incidence of respiratory failure and high mortality in cases of OP poisoning, early recognition of complicated cases and proper intensive care for patients are critical for reducing the mortality and morbidity. Because blood glucose levels can be easily and quickly measured anywhere and anytime, evaluation of the prognostic value of glycemic variables is clinically useful.

The aim of the present study was to investigate whether the initial glucose level at presentation, the mean glucose level, GV, and the frequency of hypoglycemic events during the first 3 days after admission are associated with mortality.

Methods

1. Study design

This was a single-institution, retrospective cohort study performed by chart review. The study design was approved by the Institutional Review Board at Chonnam National University Hospital (Gwangju, South Korea).

2. Subjects

The inclusion criteria allowed the participation of patients 18 years or older who presented to our emergency department (ED) after OP ingestion between 2004 and 2015. For inclusion in the study, patients should not have had co-ingestion of ethanol. Because ethanol can increase glucose levels, we excluded patients with a history of co-ingestion of ethanol and OP[16]. The patients' glucose levels should have been measured at presentation before the administration of atropine, pralidoxime (PAM), and any fluids containing glucose, or should have been measured at least 6 times every day during the first 3 days of admission. The presence of DM was determined based on a previous clinical or biochemical diagnosis of DM or treatment with oral hypoglycemic agents or insulin. Additionally, when the fasting plasma glucose level was higher than 120 mg/dl, or the postprandial plasma glucose level was higher than 200 mg/dl at discharge, the patients were considered to have DM. The diagnosis of OP poisoning was made based on the following criteria: a history of OP ingestion provided by the patient or a witness, clinical manifestations consistent with OP poisoning, decreased butyrylcholinesterase (BChE) activity, and improvement in the signs and symptoms after treatment with atropine and PAM.

The exclusion criteria were transfer of patients before the final outcome or discharge against medical advice.

All of the patients in this study received general supportive measures, which included decontamination, mechanical ventilatory support, and administration of atropine and PAM. Atropine was administered as a continuous infusion or as a bolus injection every 15 minutes and was titrated to achieve adequate atropinization including dry bronchial secretions. Additionally, 1~2 g of bolus administration of PAM was performed, followed by 0.5~1.0 g/hour for 1~3 days depending on the patient's clinical condition. The need for mechanical ventilatory support was assessed by the on-call emergency physician. The patients were weaned from the mechanical ventilator if they satisfied the hospital's criteria for weaning. After admission, if hypoglycemia (blood glucose level <70 mg/dl) was observed, 50 mL of 50% dextrose in water was administered intravenously. If the glucose level was within the range of 200~250 mg/dl, 2 U of regular insulin were administered, either subcutaneously or intravenously. For patients with a glucose level of 250~300 mg/dl, 4 U of insulin were administered, and 6 U were administered to patients with a glucose level of 300~350 mg/dl.

3. Data collection

Information on age, gender, cause of exposure, the type of OP ingested, the time interval from ingestion to arrival at the hospital, red blood cell acetyl-

cholinesterase and BChE activities, acute physiology and chronic health evaluation II score with age component depleted at 24 hours of admission (modified APACHE II), the total amount of atropine and PAM administered during hospitalization, the duration of mechanical ventilatory support, and survival outcome date was collected from a medical chart review. Modified APACHE II score was calculated to separately analyze the effect of age. The amount of OP ingested was estimated as a spoonful (5 mL), a mouthful (25 mL), a cup (100 mL), and a bottle (300 mL).

To investigate blood glucose variables, the initial glucose level at presentation and the mean glucose level, GV, and frequency of hypoglycemic events during the first 3 days of admission were obtained. The mean glucose level was calculated by averaging the glucose level measured during the first 3 days of admission. Delta glucose was calculated as a reflection of GV. Delta glucose was measured by subtracting the minimum from the maximum glucose level within the first 3 days after admission. Hypoglycemia was defined as a serum glucose level of less than 70 mg/dl[17].

4. Statistical analysis

The baseline patient characteristics are presented as frequencies for the categorical variables and as the means and standard deviation or median and interquartile range for the continuous variables. The continuous variables were compared using a t-test, or the Mann Whitney U test, according to the normality. The normality of continuous variables was tested using the Shapiro-Wilk test. Fisher' s exact test or the Chi-square test was performed to compare the categorical variables.

The receiver operating characteristic (ROC) curves were constructed to determine the optimal cut-off point of glucose variables with the highest Yuden index. For the value of AUC, the following ranges were considered: 0.8〉AUC〉0.7 indicating acceptable discrimination and AUC〉0.8 indicating good discrimination.

Multivariate logistic regression analysis was used to determine independent factors of mortality. The variables with a significance level 〈0.05 in univariate analysis and stratified glucose variables with AUC 〉0.7 were considered eligible for inclusion in the multivariate regression analysis. *P*-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 21.0.

Results

Of the 259 patients who presented to the ED after OP ingestion, 228 patients (88.0%) were included to determine if glucose variables could predict mortality and development of respiratory failure.

The baseline characteristics and clinical course of 228 patients are summarized in Table 1. One hundred seventy-two (75.4%) patients developed respiratory failure at a mean time period of 7.8 hours after presentation and needed mechanical ventilation for 9.1±13.6 days. The mortality rate was 11.4%.

Survivors were significantly younger and had higher GCS and systolic blood pressure at presentation and lower PSS and modified APACHE II score than non-survivors. With respect to the glucose variables, non-survivors had higher initial glucose levels at presentation and GV during the first 3 days of admission than survivors. In addition, non-survivors experienced a higher frequency of hypoglycemic events for the first 3 days of admission. However, the glucose level did not differ between the two groups.

The effects of the cut-off value and the AUC values of glucose variables on mortality are presented in Fig. 1. The initial glucose and delta glucose levels were predictive of in-hospital mortality with AUCs of 0.723 and 0.717, respectively, while the mean glucose level had AUCs of 0.603. The cut-off point for the initial glucose and delta glucose levels was 233 mg/dl and 78.5 mg/dl, respectively.

A multivariate logistic regression model including age, initial GCS, modified APACHE II score, the initial blood glucose level (〉233 mg/dl), delta glucose level (〉78.5 mg/dl), hypoglycemic event, PSS, and systolic BP revealed that along with age, initial blood

glucose level〉233 mg/dl (OR 16.7, 95% CI 1.286-81.554) was an independent predictive factor for in hosptial mortality (Table 2).

Discussion

In our study, an increased blood glucose level at presentation was an independent predictive factor for mortality. This result was in agreement with the results of other studies, showing that hyperglycemia upon admission is associated with increased mortality in patients with critical illness such as AMI or stroke[1-3].

In our study, 63 (31.2%) out of the 202 non-diabetic patients had an abnormally high glucose level (glucose level ≧200 mg/dL) at presentation after ingestion of OP, which was in accordance with the results of many animal studies that demonstrated hyperglycemia after acute exposure to OP[7,9].

The mechanism of impaired glucose homeostasis after OP ingestion has been investigated in recent years. The activation of the hypothalamic-pituitary-adrenal axis and the sympathetic autonomic nervous

Table 1. Baseline and clinical characteristics of 228 patients

Variables	All patient (n=228)	Survivor (n=202)	Non survivor (n=26)	*p* value
Age (years)	60.6±16.2	59.5±16.4	69.2±11.8	0.004
Male (%)	149 (65.4%)	124 (89.9%)	15 (57.7%)	0.389
Diabetes mellitus (%)	26 (11.4%)	20 (9.9%)	6 (23.1%)	0.092
The time interval from ingestion to presentation (hrs)	3.6±3.4	3.7±3.6	3.2±1.5	0.513
Intentional ingestion (%)	111 (48.7%)	97 (48.0%)	14 (53.8%)	0.738
The amount of ingestion (ml)	153.2±162.8	150.1±163.3	185.4±160.6	0.475
The type of OP* ingested (%)				0.350
Dimethyl OP	104 (45.6%)	95 (47.5%)	9 (36.0%)	
Diethyl OP	23 (10.1%)	18 (9.0%)	5 (21.7%)	
Unclassified OP	34 (14.9%)	30 (15.0%)	4 (16.0%)	
Unknown	64 (28.1%)	57 (28.5%)	7 (28.0%)	
Systolic BP (mmHg)	127.8±32.3	131.5±26.0	102.9±54.2	0.014
Initial Glasgow coma scale	10.7±4.6	11.1±4.3	7.7±5.2	<0.001
Butylcholinesterase^{+} (U/L)	2100.0±2862.7	2182.8±2961.1	1448.3±2230.0	0.252
Red blood cell acethylcholinesterase^{+} (U/L)	5068.6±4189.1	5036.3±4039.1	5301.7±5241.9	0.772
QTc >440 ms^{+} (%)	124 (54.4%)	106 (79.7%)	18 (90.0%)	0.369
Poisoning severity score	2.0±1.0	2.0±0.9	2.6±1.0	0.001
Modified APACHE II¶	10.1±7.6	9.5±7.2	16.9±8.6	0.002
Glucose variables				
Initial Glucose at presentation (mg/dl)	193.3±96.2	184.2±89.8	263.2±116.0	<0.001
Hypoglycemia for first 3 days of admission (%)	12 (5.3%)	8 (4.5%)	4 (22.2%)	0.001
Mean glucose for first 3 days of admission (mg/dl)	148.2±52.2	145.0±48.6	169.5±70.3	0.157
Delta glucose for first 3 days of admission (mg/dl)	85.1±81.0	73.1±70.3	144.6±104.9	0.015
Treatment and outcome				
Administered atropine during hospitalization (mg)	392.4±597.0	385.4±523.6	444.3±998.8	0.658
Administered PAM during hospitalization (g)	58.0±52.7	59.5±57.8	46.8±32.1	0.281
The need of mechanical ventilation support (%)	172 (75.4%)	146 (72.3%)	26 (100.0%)	0.001
Duration of mechanical ventilation support (days)	9.1±13.6	8.9±12.8	10.3±24.2	0.651
Duration of intensive care unit stay (days)	12.0±14.4	11.8±13.6	13.2±20.2	0.645

Data are presented as n (%), mean±SD for continuous variables.

OP*: organophosphate, The time interval^{+}: the time interval from ingestion to presentation, Butylcholinesterase^{+}, Red blood cell acetylcholinesterase^{+}: the normal range of butylcholinesterase and red blood cell acetylcholinesterase activity was 4,260-11,250 U/L and 11,188-16,698 U/L, respectively.

QTc^{+}: QTc value was available in 153 patients.

Modified APACHE II¶ at 24 hours: Acute Physiology and Chronic Health Evaluation II with age component depleted was calculated at first 1 day of admission.

system, reduction of glucose-induced insulin secretion from the Langerhans cells, stimulation of hepatic glycogenolysis and gluconeogenesis, induction of muscle glycogenolysis, oxidative stress, and mitochondrial impairment have been proposed as the underlying mechanisms of OP-induced hyperglycemia[11-13]. Stress leads to the release of adrenal hormones, causing enhanced release of catecholamines,

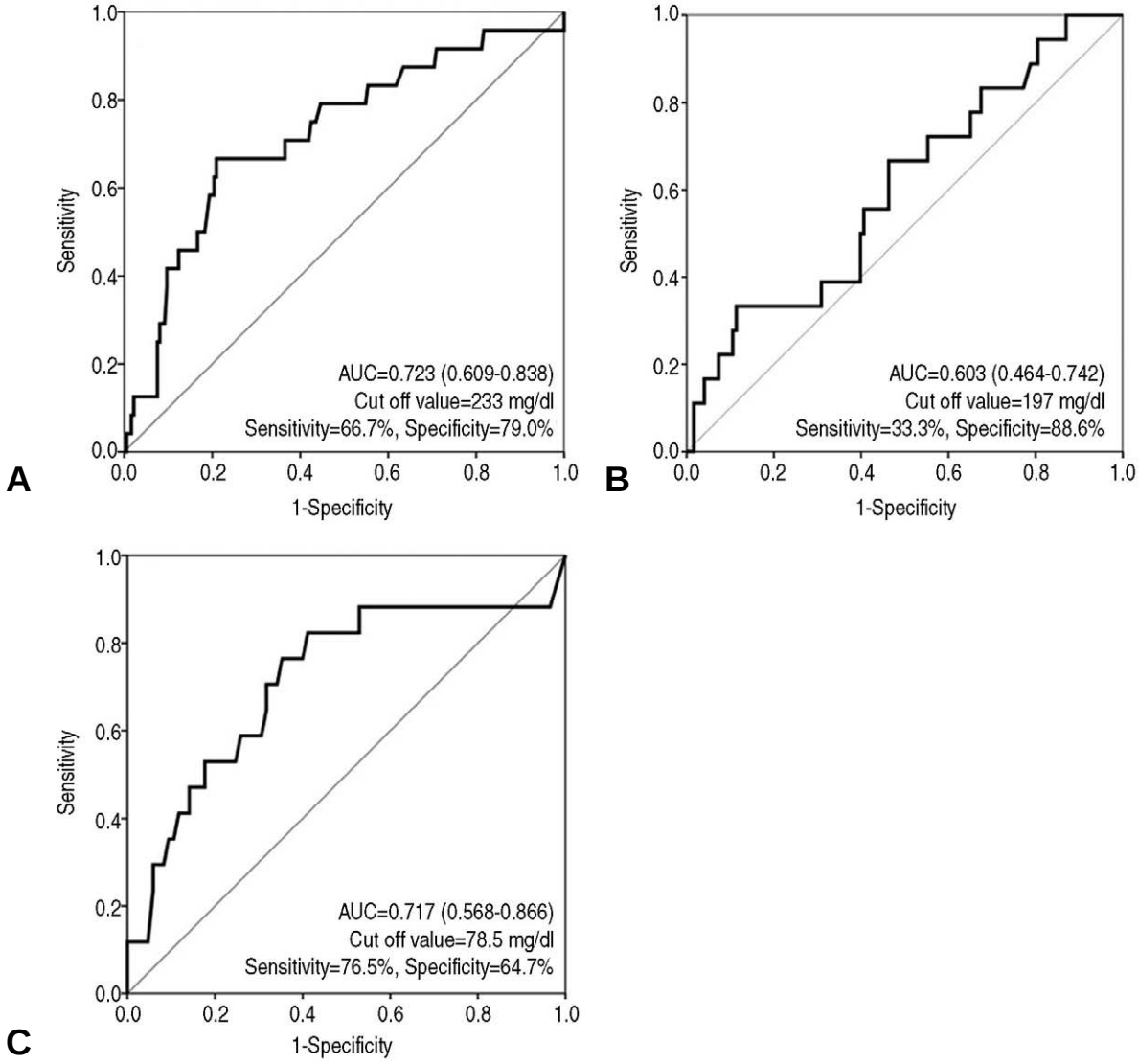

Fig. 1. Cut off values and AUC values of glucose variables (**A**: initial glucose, **B**: mean glucose during first 3 days, **C**: delta glucose during first 3 days) obtained from ROC curve analysis, showing specificity and sensitivity in the study population.
The AUCs of initial glucose level and delta glucose were more than 0.7, but the mean glucose had 0.603 of AUC. The cut off value of initial glucose level and delta glucose was 233 mg/dl and 78.5 mg/dl, respectively.

Table 2. Multivariate regression analysis including initial glucose and other significant variables which can easily be assessed at presentation for in hospital mortality

Variable	Odd ratio	95% Confidence interval	*p* value
Age	1.092	1.018-1.171	0.014
Initial glucose >233 mg/dl	16.735	2.863-97.823	0.002

glucagon, and growth hormone, and results in hyperglycemia[18]. Regardless of the mechanism for inducing hyperglycemia, hyperglycemia causes an increase in oxidative stress, impairment of leukocyte function, phagocytosis, apoptosis of cells, intra- and extracellular dehydration, and induction of inflammation, and hyperglycemia might be responsible for a worse outcome because of these unfavorable changes[19].

This study demonstrated that GV during the first 3 days, which was measured using delta glucose, was associated with mortality in univariate analysis. The effect of GV on the clinical outcome has been presented in several previously reported studies[6,20,21]. GV, which is measured by the standard deviation of the mean glucose level, was a predictor of mortality in 3252 patients admitted to the ICU and it was a stronger predictor than the mean glucose level itself[21]. The mortality rate was determined by GV in patients with identical mean glucose, and a high mean glucose level was less harmful when GV was low[6]. Although it is unclear whether GV is an epiphenomenon resulting from metabolic deterioration or the causative harmful phenomenon, acute blood glucose level fluctuation decreases the level of antioxidants and increases the level of oxidative stress markers in diabetic patients[22].

Additionally, a hypoglycemic event was associated with mortality in the univariate analysis of this study. In a recent study including 5961 patients, hypoglycemia was shown to be related to ICU mortality[23].

Considering the high mortality in OP poisoning, early recognition of patients with complications and proper intensive care are critical for reducing the mortality and morbidity. Because the blood glucose level can be easily measured anywhere, the findings of this study may be valuable for physicians treating patients with OP poisoning at presentation.

Limitations

First, this study was performed at a single center and the results may lack wider applicability. Second, the timing and frequency of glucose level measurements were not standardized in this study because of its retrospective nature. Only patients who had at least six glucose level measurements every day were included, to avoid underestimating or overestimating the glucose level during hospitalization. Even with frequent blood glucose level monitoring at regular intervals, hyperglycemia and hypoglycemia could remain undetected[24]. A prospective multi-center study, in which the glucose level in patients is continuously monitored, should be conducted. Third, the last meal could have influenced glucose levels at presentation. However, the mean time interval from OP ingestion to presentation to the ED was 3.6 hours, and the patients might not have eaten anything because of altered mentality and acute illness. As for the glucose level during the first 3 days of hospitalization, many other factors, such as antidote therapy (atropine and PAM), maintenance fluids, and total parenteral nutrition (TPN), could have influenced the glucose level and variability. However, infusion of TPN, fluids, and PAM at a constant rate made it difficult to explain the GV.

Conclusion

The initial glucose level at presentation was an independent predictor of mortality. The physician should pay attention to patients with a glucose level 〉233 mg/dl after ingestion of OP.

Declaration fo Interest

The authors report no declarations of interest.

Funding Acknowledgement

This work received no specific project grant from any funding agency in public, commericial, or not for profit sectors.

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