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Human kidney injury molecule-1 and interleukin-18 as predictive markers of nephrotoxicity in acute organophosphorus poisoned patients in Zagazig University hospitals

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Organophosphorus (OP) poisoning is a major common cause of mortality and morbidity in most countries. Some clinical cases developed renal injury after acute OP poisoning. The aim of our study is to evaluate the levels of kidney injury molecule-1(KIM-1) and interleukin -18(IL-18) in acute OP poisoned patients as early predictors of OP induced nephrotoxicity. Over a period of one year, the observational cross sectional study was conducted at the Poison Control Center, Zagazig University hospitals, Zagazig, Egypt. The study group consisted of 95 patients who fulfilled the inclusion criteria; the patients were categorized according to Peradeniya organophosphorus poisoning (POP) scale. The serum pseudocholine esterase enzyme (PChE), serum creatinine, urinary KIM-1 and IL-18 were assayed at 0, 12, 24 and 48 h after admission. There were progressive increases in the mean values of KIM-1 and IL-18 at different time intervals especially in severe poisoned patients compared to the increased levels of serum creatinine. The cutoff values of urinary KIM-1 and IL-18 that determined patients with potential AKI were 2.8 ng/ml creatinine (86.9% sensitivity, 94.6% specificity and 0.859% area under curve) and 59 pg/dl creatinine (90% sensitivity, 92% specificity and 0.946& area under curve), respectively. A positive correlation was observed between KIM-1 and IL-18 and serum creatinine. Moreover, KIM-1 is positively correlated with IL- 18. Urinary KIM-1 and IL-18 may be considered as valid markers for prediction of acute kidney injury among acute OP poisoned patients.

Key words: Organophosphorus poisoning, IL-18, KIM-1, acute kidney injury.

INTRODUCTION

Pesticides include different groups of compounds such as insecticides, herbicides, fungicides. There are many active substances incorporated in several preparations of pesticides used in agriculture. Synthesis of several organophosphorus (OP) compounds started since 1930 (Thunga et al., 2010). According to World Health

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Organization,there are 3 million cases of OP poisoning occurring every year, leading to more than 250,000 deaths. One million serious unintentional poisonings occur every year and other two million people are hospitalized for suicide attempts with pesticides (Banerjee et al., 2012; Reddy et al., 2016).

In developing countries, OP poisoning is considered as a major common problem. This is due to its easy availability and low-cost, so, it has become an agent of choice for suicide especially in rural areas (Banday et al., 2015). Exposure to it may occur through different means such as drinking, breathing or dermal exposure (King and Aaron, 2015).

Organophosphorus compounds act through irreversible inhibition of cholinesterase enzyme inducing massive accumulation of acetylcholine within the synaptic cleft. This leads to overstimulation of cholinergic receptors (nicotinic and muscarinic receptors) in the central and peripheral nervous system which occur by excess acetylcholine leading to manifestations of OP poisoning (Carey et al., 2013).

Clinically OP poisoning is characterized by acute cholinergic crisis which develops within a few minutes to hours after being exposed to it. This crisis manifests by the followings; bradycardia, hypotension, tachycardia, excess salivation/lacrimation, excessive sweating, nausea, vomiting, diarrhea, abdomenal pain, fecal and urinary incontinence (Lotti and Moretto, 1995). Central nervous system manifestations include anxiety, restlessness, convulsion, miosis, insomnia, coma, Cheyne-Stokes breathing, respiratory and cardiovascular failure (Singh and Khurana, 2009; Peter et al., 2014).

The death rate could reach 40% even with proper treatment. The main cause of death is respiratory failure (Carey et al., 2013). Other complications related to OP poisoning are motor neuropathy, arrhythmia, pulmonary edema, pneumonia, pancreatitis, and renal failure (Lee et al., 2015).

Acute kidney injury (AKI) is a problem all over the world with different causes and manifestations. Severe adverse outcomes such as high morbidity, long hospital stays, high medical cost, a risk of long-term dialysis and even late mortality can occur as a result of misidentification or underestimation of this problem (Pakula and Skinner, 2015). Acute kidney injury diagnosis is based on an absolute or percentage elevation in the serum creatinine concentration over the baseline (Waikar and Bonventre, 2009). There are many novel biomarkers for early detection of AKI such as kidney injury molecule-1 (KIM-1) and interleukin-18(IL-18) (Vanmassenhove et al., 2013).

Kidney injury molecule-1 (KIM-1) is an immunoglobulin (Ig) superfamily transmembrane receptor. It is up regulated and expressed specifically in injured proximal tubular cells to help the removal of necrotic and apoptotic debris. This expression can continue till complete recovery of the damaged cells occurs (Shao et al., 2014). Thus, KIM-1 is considered as an ideal biomarker as well as a good predictor of prognosis for kidney injury (Ahmed and Hamed, 2015). Interleukin-18 (IL-18) is a proinflammatory cytokine with a molecular weight of 18 kDa. Renal tubular cell is one of the major sources of IL-18 production. It is up-regulated and increased in cases of AKI (Gavrić and Kališnik, 2016). Therefore, this study was conducted to evaluate the urinary KIM-1 and IL-18 levels in acute OP poisoned patients as early predictors of OP induced nephrotoxicity.

SUBJECTS AND METHODS

Study protocol

An observational cross sectional study was conducted in the Poison Control Centre, Zagazig University hospitals, Zagazig, Egypt. The study was done from January 2017 to January 2018. It was done on adult patients having a history of acute organophosphorus intoxication 24 h previously and diagnosed from full detailed history given by patient or relatives, pesticide containers, thorough clinical examination and measurement of plasma cholinesterase or pseudocholine esterase enzyme level (PChE) at the time of admission. All patients were followed up during treatment.

Exclusion criteria

These include the followings:

(1) Pre-existing renal impairment
(2) Urinary tract infections (UTI) by urine analysis
(3) History or suspicion of ingestion of other poisons concomitantly.
(4) Other concomitant illness like cardiac, pulmonary and hypertension
(5)Pregnant and paediatric patients.
(6) Chronic exposure to OP.

The organophosphorus compounds were identified by the containers given by the patients or their relatives; they were chlorpyrifos in 93% cases, diazinon in 5% cases and parathione in 2% cases.

Study population

Out of 380 organophosphorus poisoned patients, 285 patients did not fulfil our criteria. 95 patients were enrolled; out of them there were 45 males and 50 females, with an average age of 18 to 50 years old. The patients were classified according to Peradeniya OP poisoning (POP) scale (Table 1) (Senanayake et al, 1993) into: (I) mild poisoned patients (n=45), (II) moderate poisoned patients (n=40) and (III) sever poisoned patients (n=10). According to POP scale, the following scores were given to the patients: a score of 0 to 3 is considered as mild poisoning, 4 to 7 as moderate poisoning and 8 to 11 as severe poisoning. Informed consents from patients were obtained.

All patients underwent decontamination and received the standard medical treatment for acute OP poisoning according to poison control centre protocol for management of OP poisoning (Eddleston and Clark, 2011). The patients were followed up till their final clinical outcome or hospital discharge.

Table 1. Peradeniya Organophosphorus Poisoning Scale (POP).

Parameter	Data	Scale
Pupil size	>2 mm	0
	<2 mm	1
	Pin point	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 or 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

Source: Senanayake et al. (1993).

The medical protocol of treatment included administration of single dose of 1 g/kg of activated charcoal, atropinisation starting with 1-3 mg then doubling doses at every 5-10 min interval. Atropine given until disappearance of chest crepitation (abolishing of muscarinic signs) was added by removing nasopharyngeal secretions and oxygen inhalation. The symptomatic cases received Pralidoxime chloride (1 to 2 g) infused over 20 to 30 min followed by 0.5 g/h for 1-3 days up to 7 days. Patients that needed to be intubated were transferred to intensive care unit (ICU).

Data collection

Data were collected by study doctors in Poison Control Centre within Zagazig University hospitals. Blood and urine samples were collected at the time of admission (0 h) before beginning treatment; 12 h from admission (12^{th}h) and daily thereafter for the next 2 days (24^{th}h and 48^{th} h) for estimation of serum PChE level, serum creatinine, urinary KIM-1and IL-18, respectively. Serum samples used for the measurement of PChE levels were collected and centrifuged using Pchem Cholinesterase reagent kit (Adaltis S.R.I., Milano, Italy) by spectrophotometer (Optizen 3220 UV, Mecasys Co., Ltd, Korea) at 405 nm according to the manufacturer's instruction. The data were expressed by U/L and the baseline reference values were 3000-9000 U/L.

Serum creatinine was measured in serum samples according to the method of (Husdan and Rapoport, 1968). using a Dimension RxLauto analyzer (Siemens Healthcare Diagnostics Inc., Newark, DE, USA). The data were expressed as mg/dl and the base line reference values were 0.7-1.2 mg/dl. A fresh mid-stream urine samples were collected using disposable cups without preservatives. The samples were immediately centrifuged, separated, and stored at-80◦C until further analysis. Urinary KIM-1 and IL-18 were measured using enzyme-linked immunosorbent assay (ELISA) (MyBioSourceMBS700484, San Diego, California, USA) according to the manufacturer's instructions. The data were expressed by ng/ml and pg/dl, respectively. All analytical procedures were done in Poison Control Centre, Zagazig University hospitals laboratories, Zagazig, Egypt.

Statistical tests

Continuous variables were expressed as mean±SD and categorical variables were expressed as a number (percentage). Data were analysed using ANOVA. Least significant difference (LSD) was used for comparison in between groups. Distribution of categorical variables was compared using the Chi-square ($\chi 2$) test. The Pearson correlation (r) was calculated to assess the correlation between serum creatinine and pseudocholine esterase, urinary KIM-1 and IL-18. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of urinary KIM-1 and urinary IL-18 with maximum sensitivity and specificity. p value <0.05 was considered statistically significant, p <0.001 was considered highly significant, and p ≥ 0.05 was considered non-significant.

RESULTS

This study included 95 patients with average age from 18 to 50 years. There were 63 patients (66.3%) with age

Table 2. Acute OP poisoning patients age distribution as a percentage.

Age range	No of patients	Percent
18-35y	63	66.3
36-50 y	32	33.7

Table 3. Demographic characteristics between acute OP poisoning studied groups using ANOVA and Chi-square statistical tests.

		Mean ±SD		Range		F	p. value
Age (29.8±10.8)	Mild	27.7±10.4		18-50			
	Moderate	32.1±11.2		18-50		3.333	0.04*
	Sever	36.2±11.3		18-50			
Sex		Males (No. =45)		Females (No. = 50)		χ2	p. value
		No.	%	No.	%		
Mild		20	44.4	25	50.0		
Moderate		18	40.0	22	44.0	2.3	0.317**
Sever		7	15.6	3	6.0		

Values are expressed as means ±standard deviation (n= 95).
* Significant (p< 0.05).
** Non significant (p> 0.05)
%: percent
F: ANOVA test
χ2:Chi-square test.

range from 18-35 years old and 32 patients (33.7%) with age range from 36-50 years old (Table 2). The OP poisoning cases were classified according to POP scale as 45 patients (47.4%) of mild toxicity and 40 patients (42.1%) of moderate toxicity and 10 patients of severe toxicity (10.5%). There was no significant difference between different groups based on gender (p> 0.05). However, comparing the mean values of age with the severity of toxicity, there was a significant increase in the mean values of age associated with severe toxicity group (p< 0.05) (Table 3).

In this study, there was a significant difference in the mean values of PChE among the studied groups at different time interval of examinations (0, 12, 24 and 48 h). There was significant reduction in the mean values of PChE in all studied groups at 0 and 12 h at the time of admission followed by gradual increase in PChE levels in both mild and moderate groups at 24 and after 48 h of admission; this approximates the laboratory reference values. However, in severe group, the mean values of PChE showed significantly lower levels when compared with mild and moderate groups during and after 48 h of admission (Figure 1).

Regarding serum creatinine levels, there were gradual unnoticeable increases in the mean values of serum creatinine, where the levels were still within the normal laboratory reference ranges at different time intervals in the studied groups. The highest levels were recorded at 48 h of admission compared to 0 h (time of admission). We also found that there were significant increases in the mean values of serum creatinine after 24 and 48 h in severe OP poisoned group compared to the mild and moderate groups (p< 0.001) (Table 4).

In comparing the mean values of urinary KIM-1 at different time intervals in different groups, its highest levels were recorded at 48 h at the time admission in all groups. The statistically significant increment was detected at 24 h in mild and moderate groups and at 0 and 12 h in severe group (p< 0.001).When different studied groups were compared with each other, we found significant differences in the mean values of urinary KIM-1 with the highest levels in the severe group (p< 0.001) (Table 4).

Meanwhile, the mean values of urinary IL-18 were compared with the time intervals among different studied groups; there were highly significant increases with the highest level at 48 h after admission in all groups. The significant increment was detected at 24 h in mild group and at 0 h in moderate and severe groups (p< 0.001). When different studied groups were compared with each other, we found significant differences in the mean values of urinary IL-18 with the highest levels in the severe

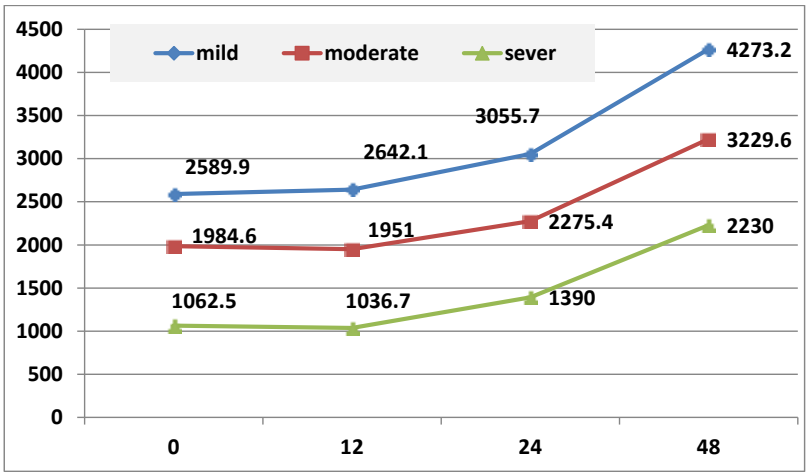

Figure 1. Pesudocholine esterase enzyme levels at different time intervals among the studied organophosphorus poisoning groups.

Table 4. Comparison between different time intervals from admission regarding serum creatinine, urinary KIM-1and urinary IL-18 levels in acute organophosphorus poisoning studied groups.

Varible	Hour	Mild Mean ±SD	Moderate Mean ±SD	Sever Mean ±SD	F	p.value
Serum creatinine (mg/dl)	0	0.551 ±0.03	0.62±0.07	0.61±0.06	15.562	<0.001**
	12	0.554 ±0.02	0.65±0.1	0.66±0.08	22.566	<0.001**
	24	0.61 ±0.1	0.68±0.1	0.83±0.07	20.158	<0.001**
	48	0.62 ±0.1	0.72±0.1	0.84±0.1	11.161	<0.001**
F		6.89	5.652	14.926		
p. value		<0.001**	0.001*	<0.001**		
KIM-1(ng/ml)	0	0.51±0.2	0.68±0.1	0.8±0.07	15.607	<0.001**
	12	0.52±0.2	0.72±0.2	2.2±0.8	95.788	<0.001**
	24	0.89±0.4	0.94±0.3	2.3±0.8	8.913	<0.001**
	48	0.94±0.4	1.3±0.09	2.8±0.7	16.54	<0.001**
F		4.454	10.775	14.409		
p. value		0.005*	<0.001**	<0.001**		
IL-18(pg/dl)	0	46.6±7.7	51.9±3.5	51.9±4.2	9.331	<0.001**
	12	49.6±2.9	54±7.8	58.3±2.9	24.513	<0.001**
	24	52.6±4.2	67.5±15.6	85.2±20.5	34.527	<0.001**
	48	60.8±12.9	67.5±17.6	86.9±19.6	11.386	<0.001**
F		29.848	15.004	17.535		
p. value		<0.001**	<0.001**	<0.001**		

Values are expressed as means ±standard deviation (n= 95).
F: ANOVA test
* Significant (p< 0.05).
**Highly Significant (p< 0.001).

group (p<0.001) (Table 4).

Regarding the correlation between PChE levels, urinary KIM-1, urinary IL-18 and serum creatinine, PChE showed significant positive correlation with IL-18 and serum creatinine. Meanwhile, it showed significant negative correlation with KIM-1. A significant positive correlation was recorded with both KIM-1 and IL-18 and serum creatinine. We also found that KIM-1 is positively

Table 5. Correlation Coefficient between pseudocholine esterase enzyme levels, urinary KIM-1, urinary IL18 and serum creatinine in acute organophosphorus poisoning patients.

Variable	KIM-1 (ng/ml)		IL-18 (pg/dl)		PChE (U/L)	
	r	p. value	r	p. value	r	p. value
PChE (U/L)	-0.125	0.015*	0.006	0.908		
Serum creatinine (mg/dl)	0.758	<0.001**	0.755	<0.001**	-0.145	0.005*
IL-18 (pg/dl)	0.699	<0.001**			0.006	0.908

r: Pearson correlation
* Significant (p< 0.05).
**Highly Significant (p< 0.001).

Table 6. Validity and accuracy of urinary KIM-1and IL-18 in prediction of AKI in acute organophosphorus poisoning patients.

	Cut -off	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy	95% confidence interval		p. value
								Lower	Upper	
KIM-1 (ng/ml)	2.8	0.859	86.9	94.6	83.3	95.9	92.6	0.737		<0.001**
IL-18 (pg/dl)	59	0.946	90	92	75	97.2	91.6	0.902		<0.001**

%: percent
PPV: Positive predictive value.
NPV: Negative predictive value.
AUC: Area under the curve.
**Highly Significant (p< 0.001).

correlated with IL-18 (Table 5). The cut-off value of urinary KIM-1 that detected patients with AKI in OP poisoned cases was 2.8 ng/ml creatnine, (area under the curve) 0.859 AUC, 86.9% sensitivity, 94.6% specificity; the positive predictive value (PPV) was 83.3 and negative predictive value (NPV) was 95.9 (Table 6; Figure 2). While the cut-off value of urinary IL-18 was 59 pg/dl, 0.946AUC, 90% sensitivity, specificity 92%; the positive predictive value was 75 and negative predictive value was 97.2 (Table 6) and (Figure 3).

DISCUSSION

Organophosphorus (OP) compounds are usually used as pesticides and are considered the commonest poison-related morbidity and mortality in our country. In our hospital, OP poisoned patients constituted the majority of admissions and this motivated us to carry out the study. Multiple organs could be affected with OP poisoning leading to worsening of clinical presentations and/ or prognosis. Renal failure may be the cause of death in some OP cases (Agostini and Bianchin, 2003). Acute kidney injury (AKI) is a sudden unexpected and sustained reduction of kidney function with several aetiologies and clinical presentations (Bellomo et al., 2001).

Acute kidney injury was reported to be frequent in severe OP poisoning (Rubio et al., 2012). A study recorded 6.17-fold higher risk of AKI among OP patients (Lee et al., 2015). Several hypotheses were proposed to explain the mechanism of AKI in OP patients, however it is unclear. An experimental study reported increase in oxidative stress, direct damage to the distal convoluted tubules, rhabdomyolysis and dehydration induced hypovolaemia (Agostini and Bianchin, 2003).

In our study, we wanted to find an association between acute OP poisoning and development of AKI within 48 h of exposure by detection of urinary KIM-1 and IL-18 as early predictors of AKI. A total of 95 patients were recruited for this study (45 males and 50 females). Majority of the patients were from rural area and their age ranged from 18 to 50 years; 66.3% were in the age group of 18-35 years (middle age). The OP poisoning severity was determined according to the POP scale from mild to severe; 47.4% of the patients were graded as mildly poisoned, with a POP score of 0-3, 42.1% of the patients were moderately poisoned (4-7) and 10.5% of the patients had severe grade of poisoning (8-11).

Our results are consistent with previous studies that used POP scale to detect OP severity among OP poisoned patients (Raikod et al., 2014; Dubey et al., 2016); they reported similar distribution of age (21-30 years) and sex (female gender) for majority of their patients. Previous studies recorded the majority of OP patients were young adults in the age group of 15-35 and 21-33 years, respectively (Khan et al., 2003; Ashray et

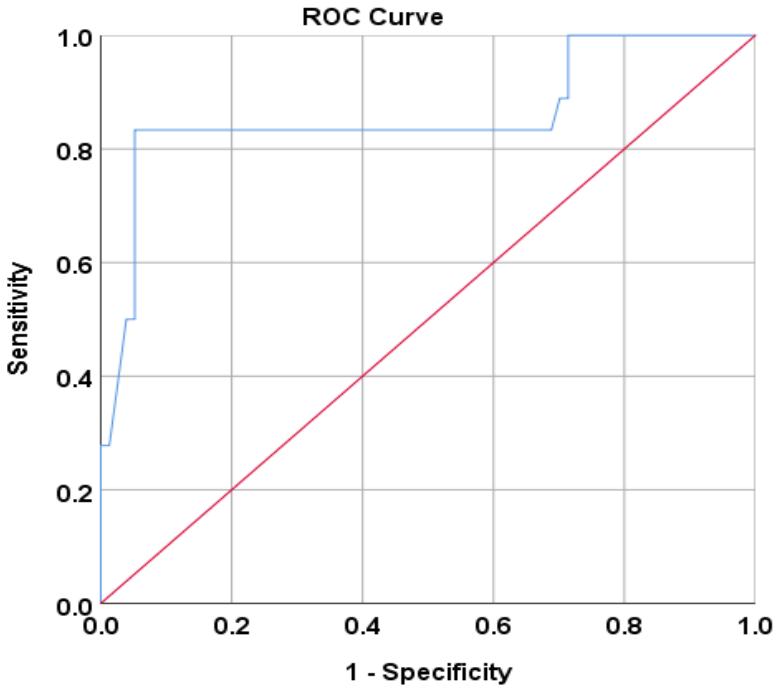

Figure 2. ROC curve to assess urinary KIM-1 as a predictor of acute kidney injury in acute organophosphorus poisoning patients

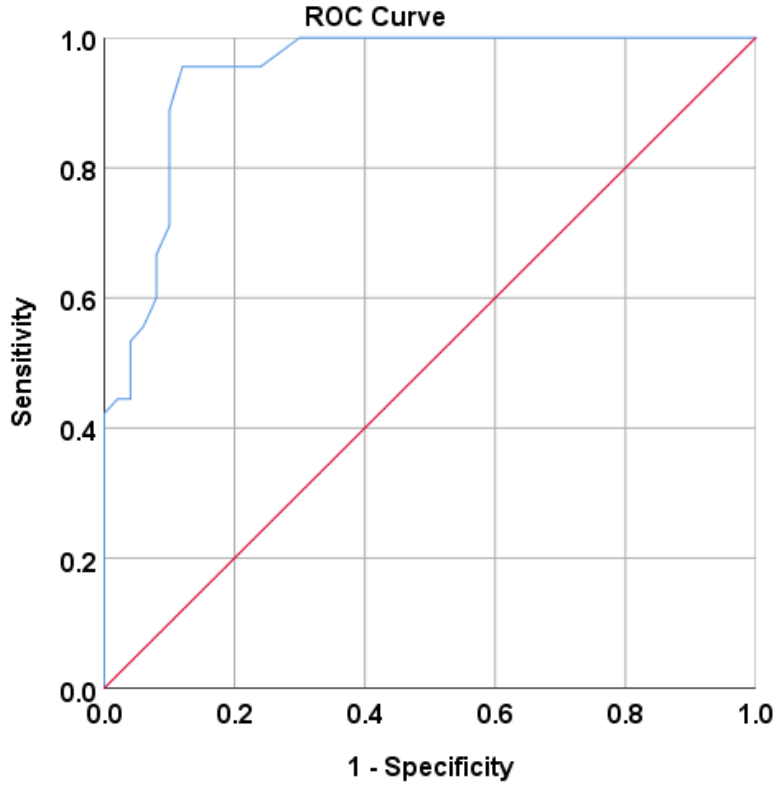

Figure 3. ROC curve to assess urinary IL-18 as a predictor of acute kidney injury in acute organophosphorus poisoning patients.

al., 2018). This age group may be attributed to the vulnerability of this age group to various emotional conflicts (Khan et al., 2003). The most dependable features for diagnosis of OP poisoning are history of exposure, miosis that has been considered a stronger indicator for OP poisoning and serum or red blood cells cholinesterase level estimation (Singh and Khurana, 2009).

In the current study, Pesudocholine esterase enzyme levels (PChE) mean values of studied groups showed lower levels in all groups at the time of admission (0 h) especially, with severe poisoned group. The mean values of PChE levels gradually increased at day two of admission; however in severe group the levels were still low. These results are in agreement with a study done by Prashant et al, on the serial measurements of serum acetylcholine esterase levels for OP poisoned cases. The study recorded gradual increment in PChE levels in moderate poisoned group while in sever poisoned group, the levels were low (Prashant et al., 2012).

Acetylcholine esterase enzyme is usually inhibited after OP poisoning resulting in increased acetylcholine in the synaptic junctions and disturbance of neurotransmission (Rovasio et al., 2011). This leads to marked reduction of both PChE and red blood cell cholinesterase activities that are considered indicators of OP excessive absorption (Prashant et al., 2012). It was suggested that PChE level could be helpful in predicting the length of ICU stay, prognosis (Prashant et al., 2012) and morbidity of OP poisoning (Ashray et al.,2018); this indicates its role in OP poisoning associated morbidity.

Our results demonstrated significant increase of serum creatinine after 24 and 48 h at the time of admission in sever group of OP poisoning compared to results of 0 and 12 h during admission. While in the mild and moderate groups of poisoning, the highest level was recorded at 48 h during admission. However during the follow up, we noticed that the levels of serum creatinine were still in the average laboratory reference ranges.

Moreover, the results of urinary KIM-1 and IL-18 showed statistically significant increase after 24 h in mild group, while in moderate and severe groups the high levels detection was earlier during admission especially, with IL-18 results. However, the severe group of OP poisoning was the most affected either with KIM-1results or IL-18 results. Our results showed that KIM-1 and IL-18 revealed the potential development of AKI earlier than serum creatinine.

Clinically AKI was defined as sudden disruption of renal function depending on elevation of serum ceratinine at a rate of ≥ 0.3 mg /dL from baseline and/ or reduction of urine output (< 0.5 mL/kg/h for more than six hours) through 48 h and staged as stage 1 injury (Mehta et al., 2007). However, it was demonstrated that about 80% of death rate increased in renal insult patients with variations of serum creatinine as little as 0.3 to 0.5 mg/dL (Uchino et al., 2006).

Unfortunately, the traditional diagnostic serum ceratinine has a limited role to be used as early predictor as its concentrations tended to be raised through 24-36 h after renal injury; if the glomerular filtration rate decreased, the half-life of serum creatinine increased from 4 h to 24-72 h and finally AKI in patients with fluid overload may be missed or delayed because the volume variations affect serum creatinine level (Liu et al., 2011). The detection and validation of new biomarkers for AKI has been progressed to replace or complement serum creatinine (Palevsky et al., 2013). These new markers could detect the little changes in renal function before serum creatinine rose (sub-clinical AKI) (Delanaye et al., 2014). The development of specific interventions made it possible to reverse AKI, if the type of injury could be diagnosed earlier (Ostermann and Joannidis, 2016).

Previous studies reported several available putative biomarkers and having the ability to provide an earlier diagnosis of AKI in humans such as KIM-1(Han et al., 2002) and (IL-18) (Melnikov et al., 2001). Human KIM-1 is from structural trans- membrane glycoprotein (339 amino acid residues in length) with an N-terminal ectodomain and may not be detectable in normal kidney tissue or urine. However it is highly expressed after renal ischemic or toxic injury in humans and animals (Zhang et al., 2007).

Urinary KIM-1 was recorded to have very high sensitivity and specificity in urine samples and is stable in frozen urine samples (Ruangyuttikarn et al., 2013). In the urine of healthy individuals, the KIM-1 levels were recorded to be less than 1 ng/ml. However, its levels after ischemic renal injury were from 3-7 ng/ml. This started to elevate as early as 6 h and remained high for 48 h after the insult (Slocum et al., 2012).

KIM-1 has been recently recognized as a biomarker for renal injury by drug and food administration in preclinical studies of pharmacological agents (Vaidya et al., 2010). It could be used as a nephrotoxic biomarker in conditions of drug induced renal ischemia (Prozialeck et al., 2007). It was reported in an experimental study on induced renal disease that urinary KIM-1 represented the tubular KIM-1expression (Shao et al., 2014).

Interleukin 18 is pro-inflammatory cytokine and is known as interferon-gamma inducing factor. It is produced by macrophage cells (monocyte) and bind to IL18 receptor to induce its action which is cell mediated immunity (Gami and Garovic, 2004). Previous studies reported that IL-18 is specific for renal tubules as its level increased with ischemic reperfusion injury (Faubel and Edelstein, 2005) and increased in AKI patients for being superior to serum creatinine in early detection (Jayaraman et al., 2014). Haase et al. (2008) attributed its increased levels for being non-specific marker that was associated with systemic inflammation rather than damage of renal tubules. IL-18 was detected as the best

predictor of the primary outcome due to deteriorated AKI or death (Arthur et al., 2014) and it could predict the deterioration of AKI when the diagnosis is based on serum creatinine (Koyner et al., 2012).

In the current study, the cut-off value of urinary KIM-1 for prediction of AKI was 2.8 ng/ml; with sensitivity of 86.9%, and specificity of 94.6%. While the cut-off value for urinary IL-18 was 59 pg/dl, with sensitivity of 90% and specificity of 92%. Wherefore, the patients with KIM-1 and IL-18 levels higher than the cut-off values were considered to have potential AKI. Previous studies on the prediction of AKI in different situations contrary to serum creatinine reported the efficiency of KIM-1 and IL-18 in early prediction of AKI before affecting serum creatinine or development of proteinuria (Liu et al., 2013; Qasem et al., 2014; Ahmed and Hamed, 2015; EL-Attar et al., 2017).

Conclusion

Urinary KIM-1 and IL-18 levels showed significant increase earlier than serum creatinine in acute OP poisoning. Urinary KIM-1 and IL-18, as non-invasive markers, were more specific in prediction of AKI in OP poisoned patients; this could be helpful in early ICU admission, prevention of renal insult and improvement of the patients.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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