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Acute Kidney Injury in Organophosphorus-poisoned Patients: The Overlooked Risk

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Abstract

Organophosphorus poisoning (OPP) is still a public health problem, especially in developing countries. Neuromuscular and respiratory complications of OPP are the most described. It is not obvious if OPP is a nephrotoxin or not. With the increasing incidence of AKI (Acute Kidney Injury), the substances that humans are daily exposed to may be accused as a cause of kidney damage. Serum creatinine does not rise before 24 hours or more of renal insults. If there are early markers for AKI, it will be definitely useful for early diagnosis and treatment of AKI with a better outcome before complications occur. In this study, we measured four biomarkers (Human alpha-glutathione S-transferases (α-GST), Human Cystatin C, Kidney Injury Molecule-1 (KIM-1), and Human Clusterine) in 48 cases of acute OPP attending to Poison Unit in Mansoura Emergency Hospital, in the first 24 hours of exposure to the OPP. Surprisingly, we found elevated levels of these biomarkers, particularly in severe OPP cases. This denotes that OPP may negatively affect the kidneys; an effect that is not in minds of the physicians, hence mostly is overlooked. Further studies are recommended, with the continuously increasing numbers of newly-manufactured organophosphorus insecticides. The earlier the diagnosis of AKI in cases of OPP provides an early treatment with a better outcome before complications occur. The further step will be the development and validation of multiplexed methods for the detection of multiple markers at the bedside for management of OPP patients.

Keywords: Organophosphorus poisoning (OPP); AKI (Acute Kidney Injury); Overlooked risk; Early markers; Diagnosis and treatment

Abbreviations: ~: Approximately; AKI: Acute Kidney Injury; ATN: Acute Tubular Necrosis; BUN; Blood Urea Nitrogen; h: hour; ICU: Intensive Care Unit; KIM-1: Kidney Injury Molecule; mg/dl: milligram per deciliter; ml: milliliter; NSAIDs: Non-steroidal anti-inflammatory drugs; ng/ml: Nano gram per milliliter; OPP: Organophosphorus Poisoning; US: United States; α-GST: Alpha Glutathione S Transferase; µg/ ml: micro gram per milliliter.

Introduction

Organophosphorus poisoning (OPP) is a frequent cause of Emergency Departments' visits. It accounts for nearly a one third of the poisoning exposures [1]. OPP is a significant health problem all over the world, especially in developing countries [2]. It causes many detrimental health effects. Neurological effects of OPP are the most described, and secondly the respiratory and the cardiovascular disturbances. Despite that these systems are the most affected by the OPP as a cholinesterase enzyme inhibitor, there are other systemic effects of this serious poisoning that may be overlooked by the physicians, hence may aggravate and be complicated. Amongst these harmful effects is the kidney injury caused by OPP [3]. Acute kidney injury (AKI) becomes a daily practice in the current medical care. AKI is a serious condition with a high risk of mortality. The term (AKI) replaced the formerly called acute renal failure (ARF) which means a rapid process kidney injury. So, the spectrum of the disease is wide, and does not only mean a group of patients who require dialysis support for kidney functions failure [4]. The standard measurements used to diagnose and monitor the progression of AKI, as serum creatinine and blood urea nitrogen levels, don not rise significantly until there is a significant kidney injury. Moreover, they are non-specific for kidney injury and can be raised in other medical conditions. Then, depending upon these measurements to diagnose AKI, there will be a substantial time delay that makes the insult more serious and difficult to treat [5].

This delay in diagnosis of AKI does not only prevent timely treatment decisions, but also significantly affects the evaluation of the toxicity of the OPP and other nephrotoxic agents, thereby allowing the nephrotoxicity to pass the preclinical stage to be detected when clinically manifest with more costs and less

favorable outcomes [6]. This necessitates the need to develop early sensitive and specific markers of renal injury, and in addition to develop a rapid high throughput technique to allow a bedside detection of multiple markers in emergency settings [5]. The early diagnosis/ prognosis of AKI in clinical settings by sensitive, specific, and reliable biomarkers will help rapid effective management of AKI and a better outcome. Further step will be the development and validation of multiplexed methods for bedside detection of multiple markers at the moment [7]. AKI is reported to complicate 20% to 50% of critical care patients, and 5- 16% of hospital admissions; Bethany et al., 2022 stated [8]. This is higher than what was reported before. AKI was reported to complicate 1 - 7% of all hospital admissions and 1- 25% of intensive care unit (ICU) admissions [9].

The incidence of AKI is showing an alarming progressive increase. In a retrospective cohort including 126528 in-patients with stage 2 or 3 AKI from US hospitals, 39% of AKI has occurred in non-ICU patients. Renal insufficiency persisted in 41% of survivors. The overall 5-year post-discharge survival was 50% and was, in this study, similar for ICU and non-ICU patients [10]. Koyner et al. (2022) see that early decisions to prevent persistence of severe AKI are important to reduce poor clinical outcomes among patients in or out the ICU [10]. Moreover, it is estimated that 20%-33% of in-hospital AKI cases are due to toxic causes. Drugs are the most believed to cause nephrotoxicity (e.g., Aminoglycoside antibiotics. NSAIDs, cisplatin; immunosuppressant drugs such as cyclosporine and tacrolimus) and environmental toxins (e.g., cadmium, mercuric chloride, poisonous snakes' bites). The OPP is usually overlooked and not thought of to be amongst the causations of acute kidney injury, despite the mechanisms of OPP toxicity can itself be a pre-renal cause of kidney injury [11].

The autonomic disturbances induced by OPP causes hypo- or hyper-tension or renal vasoconstriction that endanger the renal perfusion. OP compounds, with the increased variety of newly-manufactured types, can themselves be nephrotoxic. This results in tubular dysfunction and cell death by apoptosis or necrosis. Electrolyte disturbances resulting from fluid loss in O PP can lead to disturbance of transport functions that results in tubule-glomerular balance. Also, irritation by a xenobiotic results in inflammatory mediators release, interstitial inflammation and vascular congestion that worsen the tubule-glomerular cells injury [12]. In contrast to the heart and the brain, kidneys can efficiently restore its cells lost in an ischemic or toxic insult. However, it is believed that there are longer term detrimental effects on kidneys functions after even brief periods of AKI [13].

Diagnosis

As the serum creatinine and BUN are the tests most used to investigate for the kidney functions in most clinical settings, it is to be noted that serum creatinine does not rise in the first 24-48 hours following AKI; a time during which large changes may have happened in GFR. This results in not only delay in the diagnosis and intervention of the resulting kidney injury from the poisoning incident, but also in an underestimation of the degree of the renal injury. In addition, patients are not the same in the correlation between serum creatinine and baseline GFR, in the degree of functional renal reserve, and in creatinine synthesis rates. So, a renal injury of comparable magnitude may result in dissimilar alterations in creatinine concentration in different individuals [14]. Based on all of the above findings, there is a need to consider the risk of OPP on the kidney, and a need to early assess kidneys functions using sensitive biomarkers to allow for timely diagnosis of AKI. This will help timely treatment and the development of new therapies directed for acute renal ischemia in the context of poisoning accidents [15].

Lash (2022) defined biomarkers for early detection of AKI, like Cystatin-C, N-acetyl-β-glucosaminidase, β2-microglobulin, α1-microglobulin, Microalbumin, Retinol- binding Protein, Clusterin, Neutrophil Gelatinase-Associated Lipocalin, Kidney Injury Molecule-1, Interleukin-18, Cysteine-Rich Protein, Fatty Acid–binding Protein, Sodium/Hydrogen Exchanger Isoform, Osteopontin, Fetuin A, and others under investigations [16].

Alkaline phosphatase (AP), γ-glutamyl transpeptidase (γGT) and Alanine aminopeptidase (AAP) are markers easy to measure, and signify renal proximal tubular injury, despite that, their instability limit their clinical utility as early markers of AKI [17]. The α-glutathione-S-transferase (α-GST) also signify renal proximal tubular injury and is measured by ELISA with a stabilization buffer [18].Cystatin C is an important extracellular inhibitor of cysteine proteases. It is filtered by the glomerulus and then reabsorbed by proximal tubule cells. Its elevated urinary levels reflect tubular dysfunction; high levels may predict poorer outcome. It can be measured easily by ELISA using a serum or urine samples [19].

Kidney injury molecule-1 (KIM-1) is a type-1 cell membrane glycoprotein that is elevated in urine following AKI in preclinical and clinical studies. It is highly sensitive and specific for AKI. It is believed to be widely used as a marker of AKI in different situations [20].Clusterin, measured in urine and serum samples by ELISA, is very sensitive for AKI in preclinical models, however, still not widely used in clinical studies [21].

There are other markers that are measured by complicated procedures (e.g. Cysteine-rich protein (CYR-61; measured by western blotting, and Exosomal fetuin-A; measured by immunoblotting, and need more studies to identify their utility in diagnosing AKI [22]. There are several studies on animals and human to further identify more marker for AKI like Osteopontin (OPN) and Fatty acid binding protein (FABP) [23]. Amongst the advantages of these biomarkers is that they are easily measured in urine using immunoassay techniques. They are present also in serum. Further characterization will make these markers useful for early diagnosis of AKI in poisoned patients, hence an early treatment and a better outcome [5].

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Aim

This work aimed at screening for acute kidney injury (AKI) amongst organophosphorus- poisoned (OPP) patients, thus knowing if OPP is a risk factor for AKI.

Patients, Material and Method

This is a prospective cross-sectional study that was carried out on 48 OPP patients attending Poison Unit of Mansoura Emergency Hospital in the first quarter of 2023. The study was approved by the local ethical committee (Approval Number R.23.01.2004). Informed written consents were obtained from all patients included in this study. Forms of the approval and the consent are included later. The patients were selected amongst the attendants of Poison Unit in Mansoura Emergency Hospital, seeking treatment for pesticides exposure. Patients' age ranged from 5-82 years. Thirty-one (31) cases were male, and 17 cases were female. The median age of males was 46 years old (Range 15-82) years old. The median age of females was 30 years, range of 5- 53 years. Patients with a history of previous kidney diseases were excluded. Also, we excluded patients with concomitant other diseases, like liver, and lung diseases. Cases who received treatment of OPP another where before coming to our hospital were not selected in this study. Also, cases with other drugs co-ingestion or exposure were also excluded. Patients' severity of poisoning ranged from mild to severe degrees.

Diagnosis of Organophosphorus poisoning was made based on the history and the clinical manifestations. The five cardinal signs of OPP (miosis, increased secretions, diaphoresis, bronchospasm and bradycardia) have been assessed on a 3-point scale varying from 0-2. Poisoning can then be graded as mild (score 1-3), moderate (score 4-7) or severe (score 8-11) upon the patient's first presentation. Increased secretions include vomiting, salivation, lacrimation, urination, and diarrhea [2]. Other manifestations include the smell of pesticides or solvents, and reduced butyrylcholinesterase levels or acetyl cholinesterase activity in the blood [2]. Patients with severe Organophosphorus poisoning show disturbed consciousness and poor respiration. Carbamate poisoning is the major differential diagnosis. It is clinically indistinguishable but much milder. Many Organophosphorus pesticides are more potent inhibitors of butyryl cholinesterase than they are of acetyl cholinesterase. So, butyryl cholinesterase assays can be used to detect accurately the exposure to an organophosphates or to carbamates pesticide [1]. Grading of OPP severity into mild, moderate, and severe degrees, was done according to the plasma cholinesterase enzyme levels and the clinical picture of patients. Carbamates toxicity is clinically indistinguishable from organophosphate toxicity, but are less potent and more reversible cholinesterase enzyme inhibitors [1]. Serum samples were collected to test for the biomarkers using the ELISA technique [16].

Material

Human alpha-glutathione S-transferases (α-GST) ELISA Kit (Catalog Number. MBS702229), Human Cystatin C ELISA Kit (Catalog Number. MBS006197), KIM-1 (Catalog # MBS264966), Human Clusterine ELISA Kit (Catalog Number. MBS702592) were purchased from My BioSource, Inc., San Diego, CA 92195-3308, USA).

Methods

Sample collection

Two ml. of venous blood samples were obtained from OPP patients contributing in the study. The blood was withdrawn by simple venipuncture under sterile conditions and was left to clot then the serum was separated by centrifugation at 3000 rpm for ~ 10 minutes and aliquots were stored at -20°C until analyses are done.

Biochemical assays

These were done following the method as described in the biomarkers user manuals. Then absorbance was read using the ELISA reader capable of measuring absorbance at 450 nm.

Statistical Method

Data was tabulated, coded, and analyzed using the computer program SAS (Statistical analysis system) Enterprise Guide version 8.4. (SAS Inc., Carry, NC, USA).

Discussion

Poisoning with organophosphate compounds is still a significant public health problem, especially in developing countries. Neuromuscular and respiratory complications are the most described of the anticholinergic effects of OPP [24]. So, in this study, to get insights of further clinical characteristics of acute OPP, we investigated if OPP can cause acute kidney injury. Despite AKI was described in discrete case reports as a main presentation of poisoning with organophosphates [25,26], the protocol of management of this kind of a common poisoning has not changed over years [2]. We investigated four biomarkers in the serum of 48 acute OPP patients attending Poison Unit of Mansoura Emergency Hospital. The poisoning severity ranged from mild, moderate and severe cases (Table 1). There was no significant difference in age, sex, residence and occupation of the cases in the study. They were exposed to the OPP by different routes and modes of exposure (Table 2). Serum Creatinine was measured in all cases of the study on attendance (i.e. in the first 24 hours of exposure). Normal serum Creatinine level is 0.74 - 1.4 mg/dl for adult males, and 0.59 - 1.2 mg/dl for adult females [27].

Serum levels of α-GST, Cystatin C, Clusterin and KIM-1 were measured also in all cases of the study on attendance, and their levels were compared to their normal values and the level of serum

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creatinine in the cases (Table 3 & Figure 1). Serum creatinine was in the range of normal in all cases (Table 3). Serum α-GST was high (12.112 ± 4.436 ng/ml) in severe cases of OPP, while its levels in normal persons should be ≤ 8 ng/ml [18]. Its levels in moderate and mild cases were within the accepted levels of normal (Table 3). The same was noticed with serum cystatin C, clusterine, and KIM-1. Their levels are higher than the accepted range in normally-functioning kidneys (Table 3 & Figure 1). Serum cystatin C accepted range in normal persons should be within 0.6 to 1 µg/ml [20]. Serum clusterin normal range is believed to be 0.5 - 1.5 µg/ ml [21]. It is to be noted that KIM-1 should be undetectable or measuring less than 1 ng/ml in persons with normal kidneys [20], while it was measuring 0.585 ± 0.439 ng/ ml in severe OPP cases, and variable levels in mild and moderate cases (Table 3).

Table 1: The studied organophosphorus-poisoned cases with different degrees of severity according to their serum cholinesterase levels.

Group	Mild (n=18)	Moderate (n=17)	Severe (n=13)	p-Value
Plasma butyrylcholinesterase enzyme level (IU/ml) (Mean ±SD)	3924.944 ± 781.663	2575.882 ± 249.774	1570.385 ± 390.628	p1= <0.0001 p2= <0.0001 p3= <0.0001

p-value: Test of Significance, p1: Mild Versus Moderate Groups, p2: Moderate Versus Severe, p3: Mild Versus Severe cases, P is Significant at <0.05. Test used: multiple comparison test (Dunnett).

Table 2: Socio-demographic data and circumstances of poisoning in the cases of the study.

Sociodemographic factor	N. (%)	p-value
Age		
≤25 years n. (%)	7 (14.58%)	0.205
>25 years n. (%)	41 (85.42%)	
Residence		
Rural n. (%)	16 (33.33%)	0.478
Urban n. (%)	32 (66.67%)	
Gender		
Male n. (%)	31(64.58%)	0.905
Female n. (%)	17 (35.42%)	
Occupation		
Farmer n. (%)	22 (45.83%)	0.347
Non-farmer n. (%)	26 (54.17%)	
Mode of poisoning		
Intentional n. (%)	16 (33.33%)	0.007 (Intentional-Accidental)
Accidental n. (%)	6 (12.5%)	0.998 (Accidental-Occupational)
Occupational n. (%)	26 (54.17%)	0.004 (Occupational- Intentional)
Route of exposure		
Ingestion n. (%)	22 (45.83%)	0.81 (Ingestion-Inhalation)
Inhalation n. (%)	15 (31.25%)	0.358 (Inhalation-Dermal)
Dermal contact n. (%)	11 (22.92%)	0.826 (Dermal- Ingestion)
Severity of toxicity		
Mild n. (%)	18 (37.5%)	<0.0001 (Mild to moderate)
Moderate n. (%)	17 (35.42%)	<0.0001 (Moderate to severe)
Severe n. (%)	13 (27.08%)	<0.0001 (Severe to mild)
Number (n.); Percent (%); p-value is significant at <0.05; Test used-two sample t-test (t), multiple comparison test (Dunnett teat)		

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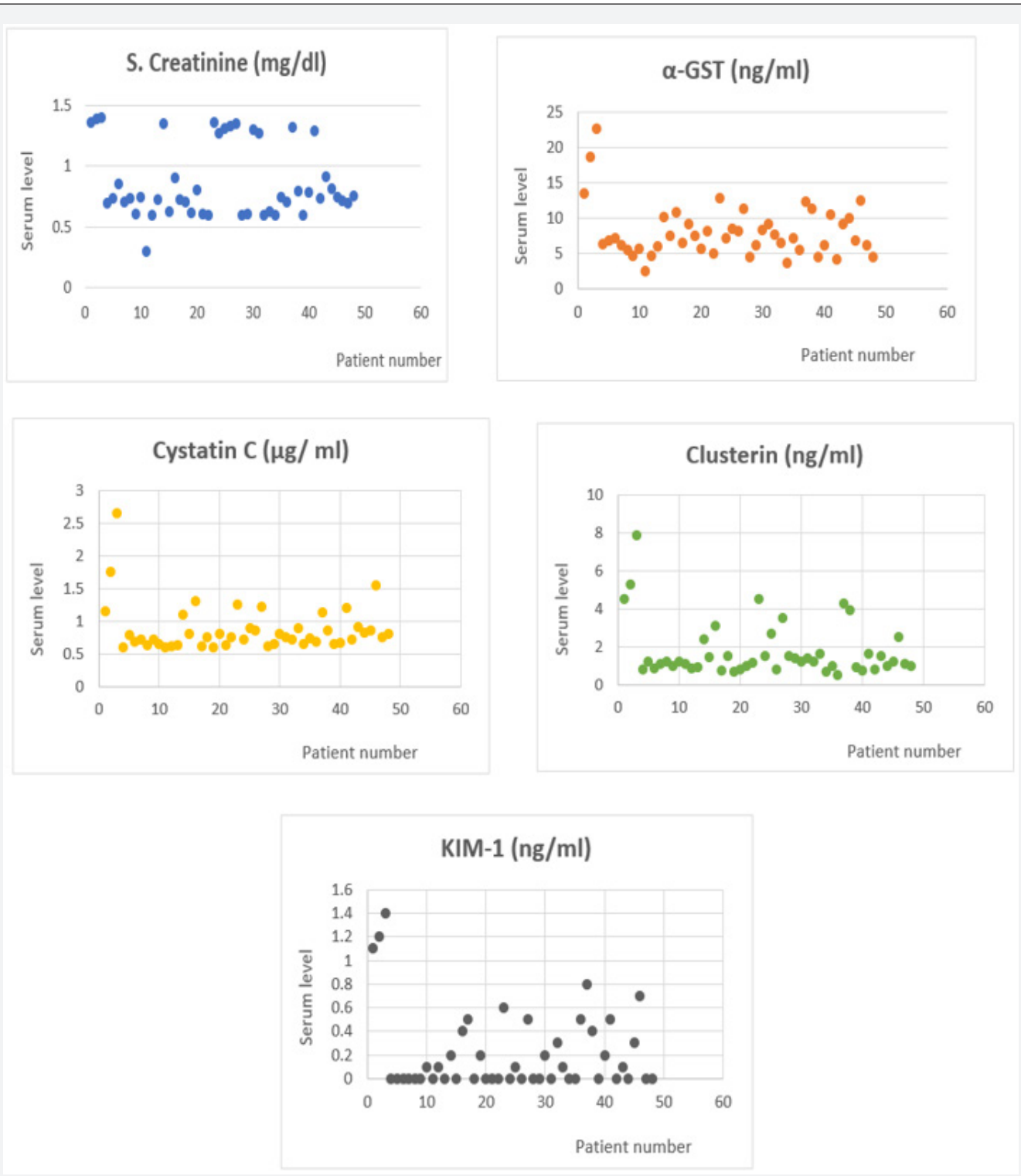

Figure 1: Serum levels of creatinine, α-GST, cystatin C, clusterin, and KIM-1 in the studied OPP cases.
(α-GST; Alpha glutathione S transferase, KIM-1; Kidney Injury Molecule-1, OPP; Organophosphorus poisoning).

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Table 3: Serum Biomarkers in Cases of Different Severity in the Study.

Biomarker Mean ± SD	Mild Cases	Moderate Cases	Severe Cases	p-Value
	(n=18)	(n=17)	(n=13)	
Serum Creatinine (mg/dl)	0.761 ± 0.229	0.801 ± 0.263	1.079 ± 0.328	p1= 0.897 p2= 0.002 p3= 0.008
α-GST (ng/ml)	6.361 ± 1.529	6.682 ± 2.257	12.112 ± 4.436	p1=0.626 p2= 0.001 p3=0.001
Cystatin C (µg/ml)	0.72 ± 0.076	0.764 ± 0.176	1.222 ± 0.538	p1= 0.904 p2=0.0004 p3=0.0001
Clusterin (ng/ml)	1.011 ± 0.285	1.308 ± 0.532	3.415 ± 1.992	p1= 0.703 p2<0.0001 p3<0.0001
KIM-1 (ng/ml)	0.1 ± 0.178	0.065 ± 0.127	0.585 ± 0.439	p1= 0.917 p2<0.0001 p3<0.0001

p-value: Test of significance, p1: Mild versus Moderate cases, p2: Moderate versus Severe, p3: Mild versus Severe cases, p is Significant at < 0.05. The test used: multiple comparison test. (Dunnett test).

Alpha-glutathione S transferase (α-GST) is an enzyme that plays a role in detoxification pathways in the liver and kidneys. Elevated levels of serum α-GST can indicate liver or kidney damage or dysfunction. This can be caused by drugs, diseases, and other factors such as strenuous exercise. So, an overall assessment of the patient's condition is done to explain the finding of elevated serum α-GST [18]. Since we excluded patients with a history of previous liver and kidney diseases, other concomitant diseases, and co-ingestions from this study. The higher serum levels of these markers than the accepted range of their levels in normal individuals, should raise attention of something disturbed in these OPP-patients. Serum cystatin C is believed not to be affected by age, sex, race, muscle mass and also does not show lag period for its rise in early AKI, unlike serum creatinine [19]. Elevated levels of KIM-1 may indicate acute kidney injury that can be caused by variety of causes, for example, nephrotoxins. However, it is important to note that KIM-1 levels can also be elevated in other conditions, such as chronic kidney disease, sepsis, ischemia reperfusion injury, ATN, cardiac arrest or shock. It should not be used as a sole indicator of kidney injury. It should be interpreted together with other laboratory tests and clinical manifestations [23].

Serum clusterin also shows elevated levels in conditions such as acute kidney injury, Alzheimer's disease, cancer, and heart disease [16]. With accurate history taking from the cases selected to this study, and exclusion of any concomitant diseases/ injuries, and co-ingestions. The elevated serum levels of the measured biomarkers in the presence of normal serum creatinine, raise attention to the possibility of a subtle kidney injury. These findings go with Jiang et al. [28] who agreed that acute organophosphorus pesticide poisoning (AOPP) can be complicated by acute kidney injury [28]. Wang et al. [29] explained the renal injury occurring after OPP by rhabdomyolysis [29]. Jiang et al. [30] explained renal and other organs' dysfunctions following OPP by cardiac arrest; endangering organs perfusion, thus impairing their functions [30]. Yu et al. [31] investigated the causes of mortality in elderly patients poisoned with OPP, and found that acute cholinergic crisis occurred in 100% of cases who died from OPP, intermediate syndrome, and delayed neuropathy occurred in some patients who died, and that these causes may precipitate a secondary organ injury that may be overlooked [31]. Bigner et al. [32] agrees to the same opinion [32]. Our findings also go with Hanif and Sattar [3] who investigated the incidence of AKI in OPP patients in Karachi National Poison Control Center in Pakistan and concluded that AKI is a common complication among patients presenting with organophosphate poisoning. They added that timely diagnosis and treatment of AKI in OPP becomes a critical issue [33].

Tajima and colleagues (2019) [34] raised attention for the necessity of testing for organs functions in the settings of drug poisoning and toxic exposures, using the novel markers rather than the routine laboratory testing markers that may not rise early in the course of organ damage. Wijewickrama and

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colleagues agreed to the same opinion [18]. Wijerathna et al. [21] found that the extent of renal injury following toxic exposures are more prevalent than we expect, and is usually missed by the physicians [21]. Since clinical examination is free in subtle kidney injury, urine output does not change and serum creatinine does not rise until the damage in kidneys is extensive, there is a need to use the early markers of kidneys injury in the early assessment of patients in Emergency Departments, and to suspect AKI from OPP in poisoning settings.

Conclusion

AKI becomes a daily medical practice, with an increasing numbers of victims of the disease. There should be an attention to what caused that increase in the incidence of AKI. Drugs use, chemicals and poisons exposure should be suspected. Organophosphorus poisoning may cause kidney damage. Early diagnosis and treatment becomes crucial to prevent more kidney damage. Biomarkers that rise rapidly in AKI becomes especially beneficial in this situation. KIM-1 and cystatin C are especially beneficial in this respect. The α-GST and clusterin may be used, combined with other biomarkers and with accurate history taking from the patient.

Recommendations

This study can be performed on a larger number of OPP patients and in multi-centers, to compare the results. New biomarkers can find their way for laboratory use in order to early diagnose kidney insults, than the routinely used markers, in the setting of poisons exposure. This will help the patients and prevent progressive kidney injury. Physicians should be aware that OPP can affect kidneys, not only the respiratory and the neuromuscular systems.

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