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Original Article

Biochemistry Section

Urinary Kidney Injury Molecule-1 as an Early Detection Biomarker for Diagnosis of Acute Kidney Injury in Patients of Snake Bite

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ABSTRACT

Introduction: Acute Kidney Injury (AKI) refers to a sudden impairment of kidney function that results in the retention of nitrogenous waste products. Acute tubular necrosis involves localised necrosis of epithelial lining in renal tubules. A soluble form of human Kidney Injury Molecule-1 (KIM-1) is a type 1 membrane-spanning protein which lends epithelial cells the capacity to perceive and phagocytose dead cells in post ischaemic kidney.

Aim: To estimate urinary KIM-1 level in patients with snake bite as a potential biomarker for early detection for AKI.

Materials and Methods: This was an analytical case-control study, which was conducted on 100 patients admitted for snake bite at Thanjavur Medical College and hospital, Thanjavur, Tamil Nadu, India, from January 2014 to August 2014. Patients without AKI were regarded as controls and those who developed AKI were considered as cases. Blood and urine samples were collected and analysed for urinary KIM-1 by Enzyme-Linked Immunosorbent Assay (ELISA), method, serum creatinine (by kinetic JAFFE'S method) and serum urea (by Urease- glutamate dehydrogenase method). Student's t-test was used and p-value <0.05 was regarded significant. Pearson's correlation coefficient was used to assess correlation between measured parameters.

Results: Among 100 patients, 44 were diagnosed as patients having AKI and 56 of them did not develop AKI. No significant difference was found in urinary KIM-1 values between age group of <40 years and age group ≥40 years in cases (p-value=0.39) and in controls (p-value=0.65). A significant elevation of urinary KIM-1 was seen among cases of snake bite who developed AKI. Urinary KIM-1 levels were found to significantly rise within 24 hours of admission (p-value <0.001), whereas, serum creatinine and urea values were not increased until the day 3 of nephrotoxic trauma. The urine KIM-1 and serum creatinine on day 1 had negligible correlation (r-value=0.093, p-value=0.54) and urine KIM-1 and urea on day 1 had low positive correlation (r-value=0.380, p-value=0.011). With progressive damage to the kidneys, a positive correlation was found between urine KIM-1 and serum urea (r-value=0.864), creatinine (r-value=0.882) on third day. Also, levels of urinary KIM-1 significantly increased (p<0.001) with the severity of tubular injury.

Conclusion: Urinary KIM-1 is a promising quick predictive marker of AKI in contrast to traditional markers, serum urea and creatinine.

Keywords: Acute tubular necrosis, Serum creatinine, Serum urea

INTRODUCTION

Acute kidney injury is a syndrome, characterised by a swift reduction in the GFR over hours to days. Acute kidney impairment or injury includes the entire spectrum that ranges between slightest elevation in the serum creatinine level, and kidney failure with complete anuria [1]. Of late, there has been a high preponderance of AKI. The yearly incidence rate of AKI in the general population is 7% and mortality associated is high [2]. In the rural areas of developing countries, among agricultural workers and farmers, snake bite is a common occupational hazard.Viper bites have been more common among venomous snakes in India [3]. The ARF causing vipers which are widely distributed in India are Russell's viper and Echiscarinatus [4].

Being well vascularised organs, the kidneys, show a high susceptibility to the snake venom toxin. The renal histopathological changes that were most significantly seen in AKI due to snake envenomation were acute tubular necrosis (100%) and acute cortical necrosis (25%) [5]. Following envenomation AKI develops within one to two days [6]. The pathogenesis of renal injury is contributed by bleeding, hypotension, intravascular haemolysis, haemoglobinuria circulatory collapse, direct nephrotoxicity of venom, disseminated intravascular coagulation, microangiopathic haemolytic anaemia, andrhabdomyolysis [3]. Snake venom induces AKI either by its direct cytotoxic effect on the kidneys or by a secondary reaction to systemic envenomation triggered by inflammation, release of cytokines (interleukins, TNF-α) and vasoactive substances like Bradykinin, Histamine, Nitric oxide and Eicosanoids. Usually snake venom induced kidney injury can be reverted, but once acute cortical necrosis develops, it may culminate in irreversible kidney damage [3].

Kidney injury molecule-1 (KIM-1) is a membrane spanning protein present in the renal tubules whose expression gets markedly induced in acute nephrotoxic kidney injury [7]. The KIM-1 is a member of the Immunoglobulin gene Super Family (IgSF), which is structurally very similar to Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1) [8]. It is a type-1 membrane glycoprotein with a molecular weight of 104 kDa and has an extracellular segment, containing a domain alike immunoglobulin with unique six-cysteine residues, a mucin domain where O-glycosylation of the polypeptide can occur and two putative sites of N-glycosylation [9].

In addition it also contains a membrane spanning domain, and a comparatively small intracellular segment containing a highly preserved site for phosphorylation by tyrosine kinase. This suggests that KIM-1 could be a signaling molecule due to the presence of tyrosine kinase activity in the cytoplasmic domain [7,10]. As an early response to kidney injury, there is a dramatic upregulation of KIM-1 in the dedifferentiated epithelium of proximal convoluted tubules [10]. Consequently, the highly glycosylated extracellular segment of KIM-1 is shed from the cellular surface into the lumen of the tubules [9]. This casting off of the glycoprotein by proteolytic cleavage, brings about the delivery of a soluble structure of molecular weight 90 kDa into the lumen, leaving the C-terminal stalk retained within the cell

[11]. Study by Vaidya VS et al., suggest that the ectodomain which is shed in the urine can be sufficiently stable for a prolonged time period [12]. The close correlation between KIM-1 expression in the tissue and its urinary excretion adds to the usefulness of KIM-1 as a biomarker of AKI [13]. Thus, this study was conducted to estimate urinary KIM-1 level in individuals with snake bite with AKI and make a comparison between the levels of urinary KIM-1 and, serum creatinine and urea. The aim of the study was to assess the utility of urinary KIM-1 as an early biomarker of AKI in patients of snake bite.

MATERIALS AND METHODS

This was an analytical case-control study which was conducted from January 2014 to August 2014 at Thanjavur Medical College, Thanjavur, Tamil Nadu, India. The methods and procedures done were in correspondence with the ethical standards of the Institutional Ethical Committee (IECC approval no.007 dated 06.12.2013, Thanjavur Medical college, TN Dr. MGR Medical University). As per the minimum study requirements and the feasibility of patient availability as per the inclusion criteria, convenient sampling method was chosen for sample collection.

Inclusion and Exclusion criteria: Both males and females above 18 years of age, were included after obtaining an informed consent from each of them. Snake bite patients with elevated serum creatinine on admission, patients with chronic kidney disease, history of diabetes mellitus, known hypertensive patients on treatment, history of nephrotic syndrome and polycystic kidney disease were excluded from the study.

The study population was divided into two groups. The patients who developed AKI within 12 hours of snake bite were regarded as cases and those without AKI following snake bite were regarded as controls .A detailed history was taken regarding snake bite location, time of bite, species of the snake, any kind of treatment taken prior to hospitalisation, presence co-morbid diseases and concomitant drug intake, history of reduced urine output, infections and fever.

Physical examination for local as well as systemic signs of envenomation such as fang marks, bleeding, blistering, necrotic or gangrenous changes at the site of bite, cellulitis, regional lymphadenopathy, ecchymosis, epistaxis and bleeding of gums was done.

Study Procedure

Urine samples were collected on the day of admission in sterile tubes and centrifuged for 20 minutes at a speed of 2000 rpm. The storage of supernatant was done at -20°C. Centrifugation was repeated for those samples in which sediments developed during storage. Urinary human KIM-1 was estimated by Enzyme-Linked Immunosorbent Assay (ELISA) which was a Biotin double antibody sandwich-based kit. The KIM-1 values of less than 1 ng/mL were considered to be normal. The patients diagnosed with AKI were further staged for severity based on KDIGO criteria referred from KDIGO Clinical Practice Guideline For Acute Kidney Injury, Kidney International Supplements (2012). Patients whose SCr was 1.5-1.9 times the baseline were grouped stage 1, SCr 2-2.9 times the baseline as stage 2 and SCr 3 times the baseline or increase in SCr ≥4 mg/dL as stage 3 AKI. The samples were also estimated for serum creatinine by spectrophotometric kits based on Modified Jaffe's reaction, serum urea was based on urease method (Glutamate Dehydrogenase-fixed) by fully automated biochemical analyser (EM 360, Transasia), complete blood count and clotting time.

STATISTICAL ANALYSIS

The analysis of data as done using Student's t-test. The data werereported as mean and standard deviation. In all analysis p-value <0.05 was considered significant. Correlation among the measured parameters was assessed by Pearson's correlation. Among groups of patients with different stages of AKI, the difference in mean urinary KIM-1 levels was assessed using one-way Analysis of Variance (ANOVA) test.

RESULTS

Overall, 100 subjects participated in the study. Urinary KIM-1 levels were estimated within 24 hours of admission. The samples were also tested for serum creatinine and ureaon the day of admission as well as on the third day. The stages of AKI was interpreted using KDIGO (Kidney Disease: Improving Global Outcomes) criteria.

Among 100 patients, 44 were diagnosed as patients having AKI and 56 of them did not develop AKI. [Table/Fig-1] shows the baseline characteristics of all the subjects enrolled in the study.

Baseline characteristics		Controls (n,%)	Cases (n,%)
Age (years)	<40	52,52%	60,60%
	≥40	48,48%	40,40%
Sex	Male	52,52%	64,64%
	Female	48,48%	36,36%

[Table/Fig-1]: Baseline characteristics of cases and controls. There was no statistical significance observed between the groups.

[Table/Fig-2] shows the comparison of KIM-1 levels in urine between age group of <40 years and ≥40 in cases and controls. No significant difference was found in urinary KIM-1 values between age group of <40 years and age group ≥40 years in cases (p-value=0.392) and in controls (p-value=0.62).

	Urinary KIM-1			
	Controls (ng/mL)		Cases (ng/mL)	
Age group	Mean	SD	Mean	SD
<40 years	0.52	0.28	4.44	2.44
≥40 years	0.57	0.19	5.37	2.7
p-value (t-test done)	0.62		0.392	

[Table/Fig-2]: Comparison of urinary KIM-1 levels in urine between age group of <40 years and ≥40 years in cases and controls with snake bite.

[Table/Fig-3] the comparative levels of urinary KIM-1 in males and females among cases and controls. A significant difference was found in mean urinary KIM-1 levels between males (5.6 ng/mL) and females (2.7 ng/mL) among cases (p-value=0.001). However, among controls a significant difference in mean urinary KIM-1 values was not found (p-value=0.9) between males (0.53 ng/mL) and females (0.55 ng/mL).

	Urinary KIM-1			
	Controls (ng/mL)		Cases (ng/mL)	
Sex	Mean	SD	Mean	SD
Male	0.54	0.27	5.6	2.37
Female	0.56	0.21	2.7	1.24
p-value (t-test done)	0.9*		0.001**	

[Table/Fig-3]: Comparison of urinary KIM-1 concentration between males and females. *p-value >0.05 was considered statistically insignificant; **p-value ≤0.001 was considered statistically significant

[Table/Fig-4] shows the comparison of urinary levels of KIM-1 on the day of admission among cases and controls. The mean urinary KIM-1 levels among cases (4.8 ng/mL) was significantly greater (p-value <0.001) than the values obtained in control group (0.5 ng/mL).

Urinary KIM-1 (ng/mL)	Range (ng/mL)	Mean±SD (ng/mL)	p-value (t-test done)
Controls	0.1-0.9	0.54±0.23	<0.001
Cases	1.2-8.9	4.8±2.52	

[Table/Fig-4]: Comparison of urinary KIM-1 among cases and controls on day of admission.
p-value ≤0.001 was regarded highly significant

[Table/Fig-5] depicts comparative difference of serum creatinine levels on first as well as third day between cases and controls. No significant

change (p-value=0.35) was was observed in mean serum creatinine levels on the day of admission between cases (0.87 mg/dL) and controls (0.81 mg/dL). On the third day, the mean serum creatinine levels were significantly higher (p-value <0.001) in cases (3.2 mg/dL) as compared to controls (mean was 1.03 mg/dL) with p-value <0.001.

Serum creatinine (µmol/L)	Controls	Cases	p-value (t-test done)
	Mean±SD	Mean±SD	
Day 1	0.81±0.18	0.87±0.17	0.356*
Day 3	1.03±0.22	3.15±2.23	0.0001**

[Table/Fig-5]: Comparison of serum creatinine concentration on day 1 and day 3 admission among cases and controls.
*p-value >0.05 was regarded statistically insignificant; **p-value ≤0.001 was regarded as statistically significant

[Table/Fig-6] reveals a comparative difference in serum urea levels on first and third day between cases and controls. No significant change (p-value=0.607) was observed in mean serum urea levels on the day of admission in cases (33.6 mg/dL) as compared to controls (32.5 mg/dL). On the third day, mean serum urea levels were significantly elevated (p<0.001) in cases (86.7 mg/dL) as compared to controls (41 mg/dL).

Serum urea (mg/dL)	Controls	Cases	p-value (t-test done)
	Mean±SD	Mean±SD	
Day 1	32.5±6.67	33.6±7.27	0.61*
Day 3	41±9.88	86.7±40.4	<0.001**

[Table/Fig-6]: Comparison of serum urea concentration day 1 and day 3 of admission among cases and controls.
*p-value >0.05 was regarded as statistically insignificant; **p-value ≤0.001 was regarded as statistically significant

[Table/Fig-7] depicts the correlation between urinary KIM-1 and the traditional renal biomarkers serum creatinine and serum urea on first and third day among cases with snake bite using Pearson's correlation coefficient. The analysis revealed that urinary KIM-1 was not significantly correlated to serum creatinine and serum urea on the day of admission. However, a significant positive correlation was observed on the third day.

Correlation between	Correlation coefficient	Correlation	p-value
KIM-1 and creatinine on day 1	0.093	Negligible correlation	0.54*
KIM-1 and creatinine on day 3	0.882	High positive correlation	<0.001***
KIM-1 and urea on day 1	0.380	Low positive correlation	0.011**
KIM-1 and urea on day 3	0.864	High positive correlation	<0.001***

[Table/Fig-7]: Pearson's correlation between urinary KIM-1, serum creatinine and urinary KIM-1, serum urea.
*p-value=0.05 was regarded as statistically insignificant; **p-value ≤0.05 as statistically significant; ***p-value ≤0.001 as highly statistically significant

[Table/Fig-8] shows the comparison of urinary KIM-1 levels in each stage of AKI based on KDIGO staging. The ANOVA test was employed to compare the difference in mean urinary KIM-1 levels among groups with stages I, II and III of AKI following snake bite. A significant difference (p<0.001) was found between mean KIM-1 values of stage 1 (2.03 ng/mL), stage 2 (4.3 ng/mL) and stage 3 AKI (7.8 ng/mL).

Stages of AKI	Number of patients	Urinary KIM-1 values (ng/mL) Mean±SD	Standard error
Stage 1	14	2.03±0.66	0.23
Stage 2	14	4.3±0.71	0.25
Stage 3	16	7.8±0.8	0.26
p-value		<0.001	
F statistic		135.36	
Degree of freedom		2	

[Table/Fig-9]: Distribution and urinary KIM-1 values of patients with various stages of AKI and Difference in mean KIM-1 concentration between groups of patients of various stages of AKI by ANOVA test.

DISCUSSION

The AKI is a frequent cause of morbidity in hospitalised patients. Thus, novel biomarkers with higher sensitivityare needed to detect early kidney injury. So far, to detect AKI, serum creatinine has been the standard test. However, rise in serum creatinine can be determined only after the death of about 50% of renal cells has happened and its concentration is relatively not sensitive to minorvariations in GFR. Therefore it isn't a suitable test for early identification of AKI.

Consequently, better biological markers of AKI are needed, for early detection of AKI, to spot the severity of insult and to direct the management.

The present study evaluates the utility of urinary KIM-1 as a novel marker to detect AKI at the earliest in comparison to the conventional markers, serum urea and serum creatinine. On the day of admission, among participants with snake bite, the mean KIM-1 concentration in urine, among cases (who developed AKI) was significantly greater (p<0.001) as compared to the control group (who did not develop AKI), as explained in a study by Bonventre JV, [9]. Comparison of serum creatinine between cases and controls revealed that on day 1 there was no significant difference (p-value=0.35), but on day 3 it was significantly elevated among cases (p-value <0.001). Similarly, serum urea was found to be significantly elevated among cases only on day 3 (p-value <0.001) as compared to day 1 (p-value=0.607). The present study reveals that increase in serum urea and serum creatinine level is observed only on day 3 of nephrotoxic insult, whereas urinary KIM-1 levels escalate much earlier than the conventional biomarkers such as serum creatinine and serum urea. These findings were supported by the study of Vaidya VS et al., [12]. Comparison of KIM-1 levels between groups of participants <40 years and ≥ 40 years of age revealed that both among cases (p-value=0.39) and controls (p-value=0.62) there was no significant difference. So, urinary KIM-1 was not influenced by age, as supported by the study done by Pennemans V et al., [10]. Further, comparison of KIM-1 levels between male and female participants showed that, among cases the mean levels were significantly higher (p-value=0.001) in males than females, however among controls no significant difference was found (p-value=0.91). This was in contrary to the finding of the study done by Pennemans V et al., who proved that urinary KIM-1 was not influenced by age [10].

Also, it was found that negligible correlation was observed between urinary KIM-1 and serum creatinine (r-value=0.093, p-value=0.54), and a low positive correlation between urinary KIM-1 and serum urea on the day of admission (r-value=0.380, p-value=0.011). Progressive damage to the kidneys resulting in surge of serum creatinine concentration, reveals a significant high positive correlation of KIM-1 levels with serum creatinine (r-value=0.882, p-value <0.001), as well as serum urea (r-value=0.864, p-value <0.001) on day 3. Hence, urinary KIM-1 is elevated in early stages of AKI which is in correlation with findings of study done by Yuzhao Zhou et al., [14]. Additionally, the cases of snake bite who developed kidney injury were grouped as stage I, stage II and stage III AKI, based on KDIGO staging for AKI. It was found that there was a significant difference (p-value <0.001) between the mean KIM-1 concentration of cases with stage I (2.03 ng/mL), stage II (4.3 ng/mL) and stage III AKI (7.8 ng/mL). These findings reveal that urinary KIM-1 levels increase with severity of kidney injury.

The above results reveal that urinary KIM-1 is responsive to slight disruption in kidney function, a specific and non invasive procedure for rapid detection of AKI compared to conventional markers such as serum urea and serum creatinine [15]. KIM-1 values in the urine significantly increase with the severity of tubular injury as inferred by ANOVA test (F-ratio135). In case of acute ischaemic tubular necrosis, urinary KIM-1 is a very effective biomarker to detect kidney injury in a day [16,17]. Following an acute tubular injury, the epithelial cells of proximal tubules are de-differentiated and the expression of KIM-1 is significantly upregulated. The highly glycosylated ectodomain of

KIM-1 is cast off from the exterior of the cell into lumen of the tubules by matrix metalloproteinases, following which a soluble 90 kDa form gets expelled in the urine [11].

In addition to this, the distinctive traits of KIM-1 that make it ideal as a biomarker are that its expression is limited to cells of injured proximal tubules of kidney and is virtually absent in healthy kidneys. The rapidly severed ectodomain that sheds into the tubular lumen makes it appreciable in urine. So KIM-1 may serve as a non invasive, rapid, sensitive and consistent marker to assess renal injury in urine [18,19]. Furthermore, it plays a prognostic role in predicting renal insufficiency. Following toxic or ischaemia kidney injury, urinary KIM-1 detection in less than 12 hours makes it an early diagnostic tool compared to serum urea and creatinine [20]. Despite repeated freeze-thaw cycles, KIM-1 has been found to remain stable in urine, hence it has the advantage that stabilising buffer is not needed to check its degradation while storing samples [14,21]. As the behaviour of KIM-1 in humans is similar to that in animals, it is established as a 'true translational biomarker' for developing drugs, evaluating toxicity of new candidate therapeutics and kidney safety monitoring. The EMEA and FDA have added KIM-1 in the list of kidney injury biomarkers to evaluate kidney damage as part of drug review processes of new drugs [9,22].

Limitation(s)

The present study is limited by small sample size. Further, urinary KIM-1 was analysed only on the first day of admission. It is not known whether urinary KIM-1 levels show fluctuations with time.

CONCLUSION(S)

In the present study on snake envenomation patients, urine KIM-1was found to be a promising quick predictive marker of AKI as compared to traditional biomarkers like serum urea and serum creatinine. This novel biomarker facilitates early diagnosis of AKI and to make decision regarding management that includes administering specific preventive and therapeutic schemes, henceforth reducing morbidity and mortality associated with AKI.

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