ORIGINAL ARTICLE

EARLY DIAGNOSIS OF ACUTE KIDNEY INJURY BY URINARY NEUTROPHIL GELATINASE ASSOCIATED LIPOCALIN IN ADULT CRITICALLY ILL PATIENTS

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Background: Acute kidney injury (AKI) is a major cause of mortality and morbidity in the hospitalized patients. It is also a risk factor for chronic kidney disease and advance renal failure. Early diagnosis with new biomarkers for AKI can prevent and/or reverse the process before rise in serum creatinine and symptomatic renal failure. This study is aimed at the accuracy of Urine neutrophil gelatinase associated lipocalin (NGAL) for detection of AKI at an early stage. **Methods:** It is a descriptive, cross sectional study conducted in the Medical Intensive Care Unit of Shifa International Hospital, Islamabad. Total 97 patients admitted in intensive care unit, age from 18–75 years, fulfilling the inclusion criteria were included by non-probability, consecutive sampling technique. Duration of study was six months, from 1st February 2014 till 31st July 2014. Urine samples of study population were tested for NGAL and simultaneously serum creatinine levels were checked, which were repeated at 48 hours for diagnosis of AKI. Patients with AKI and positive values of NGAL were considered true positive while patients without AKI and negative values of NGAL were considered true negative. Accuracy of NGAL was then calculated and effect modifiers like age and gender checked by chi square testing. **Results:** Mean age of the participants was 57.76 years with the range of 26–74 years. Out of the total population of 97 patients, 48.5% were males and remainder 51.5% were females. The study found that the accuracy of the urinary NGAL in diagnosis of AKI when compared with serum creatinine was 90.7%. **Conclusion:** Urine NGAL is an accurate marker of AKI in critically ill patients. Therefore, it should be included in the diagnostic workup of AKI in early stages.

Keywords: Urine neutrophil gelatinase associated lipocalin (Urine NGAL); Acute kidney injury; Serum creatinine; critically ill patients

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INTRODUCTION

Acute kidney injury (AKI) is a frequent and serious complication in all hospitalized patients and associated with significant mortality and morbidity.[1] In critically ill patients admitted in intensive care units (ICU), prevalence of acute kidney injury is up to 60%.[2] Acute kidney injury in ICU is associated with increase length of hospital stay, dialysis initiation and increased death.[3]

Early detection of AKI is important, as early intervention and regime modification can prevent further renal injury and improve renal outcome[4]. The current guidelines for detection of AKI depends upon serial serum creatinine values. It is also known that serum creatinine rises about 24 to 48 hours after renal injury has occurred and serum creatinine is dependent upon other factors like hydration status, muscle mass and diet. Therefore, it is important that kidney injury is identified earlier, so that timely intervention and regime modification is done to prevent further kidney injury.[4]

Neutrophil gelatinase-associated lipocalin (NGAL) was initially found in activated neutrophils. It is a potential marker for AKI, which has been identified with the help of genomic and protein micro-array technology. Several recent clinical studies have reported encouraging predictive properties of NGAL for AKI development.[5] Urinary NGAL can identify kidney injury in its early phase, 24–48 hours before rise in serum creatinine with sensitivity of 84.6% and accuracy of 93.3%.[6] It can also identify patients that are most likely to require renal replacement therapy. Several studies have shown that NGAL remains normal in prerenal AKI secondary to dehydration. This has important implications as liberal fluid replacement can reverse the renal injury.

Acute kidney injury in ICU patients has not been studied well in our part of the World. One study showed that prevention of this disastrous complication appears to be better than treatment once it is fully established.[7] Mortality among those who developed AKI was 88.8%.[7] Therefore, a new biomarker is needed for early detection and prevention of AKI in critically ill patients. Data regarding use of Urinary NGAL for early detection of AKI is lacking among ICU patients in local

population. This study helped us in understanding the clinical application of NGAL in our patients, and it also helped us in recommending use of NGAL locally so that AKI can be detected in its early stage and prevented by regime modification.

MATERIAL AND METHODS

It is a descriptive, cross sectional study. After seeking the approval of hospital ethical committee, the study was conducted at Medical Intensive Care Unit, Shifa International Hospital, Islamabad, from 1st February till 31st July 2014. Total sample size was 97 patients. Non-probability, consecutive sampling technique was used. Adult patients >18 years and <75 years of age, admitted in ICU and having urine output of less than 0.5 ml/kg/hour for 3 hours were included. Patients with established AKI, chronic kidney disease, patients on haemodialysis and renal transplant were excluded. Written informed consent was taken from participants fulfilling the inclusion criteria. The aims, nature and procedures of the study were fully explained to the potential study population.

Urinary samples for NGAL levels of study population, fulfilling the inclusion criteria, were sent immediately to the laboratory. The test was run on Abbott's Architect Kit and results were verified by a qualified pathologist. Simultaneously, all the blood samples for serum creatinine levels were also sent to laboratory. Tests were run using Kinetic Alkaline Picrate Kit of Abbott and results verified by the pathologist. The AKIN criteria (Annex A) was used to diagnose AKI in critically ill patients. A specially designed *pro forma* was used to record patient's age, gender, urine NGAL values, creatinine values at 0 hour and 48 hours, true positive and true negative cases. All the data was entered and analysed using SPSS version 12. Mean and standard deviation were calculated for continuous variables like age, urine NGAL and serum creatinine. Frequencies and percentage were calculated for categorical variables like gender and true positives. Effect modifiers like age, gender were controlled by stratification. Post stratification chi^2 test was applied. *p*-value equal or less than 0.05 was considered significant.

RESULTS

A total of 97 patients were enrolled in this study. Mean age of participants was 57.76 years with standard deviation of ±11.168 and range of 26–74 years. Amongst the participants, 47 (48.5%) were male and 50 (51.5%) were females. Mean of NGAL was 735.57 ng/ml with a standard deviation of ±1211.43 and range of 10 ng/ml to 6000 ng/ml. Accuracy of NGAL was calculated in terms of percentage of all the true positive and true negative cases. There were total of 71 cases (73.2%) that were true positive and 17 cases (17.5%) were true negative (Table 1). The accuracy of NGAL in this study was 90.7% (Table-2). Mean creatinine value at 0 hour was 1.02mg/dl with standard deviation of ±0.24 while mean creatinine at 48 hours was 2.01mg/dl with standard deviation of ±1.01. Age and gender were controlled by stratification and post stratification chi square test was applied. The test revealed chi square value 4.180 for age groups and accuracy with *p*-value 0.52 while for gender the test revealed chi square value 1.318 with a *p*-value 0.251 where *p*-value of less than 0.05 was considered significant. (Table-3)

Table-1: Percentage of true positive and true negative

	Frequency	Percent	Valid Percent
True positive	71	73.2	73.2
True negative	17	17.5	17.5
False positive	1	1.0	1.0
False negative	8	8.2	8.2
Total	97	100.0	100.0

Table-2: Accuracy of urine NGAL (%age)

	Frequency	Percent	Valid Percent
Yes	88	90.7	90.7
No	9	9.3	9.3
Total	97	100.0	100.0

Table-3: Chi-Square tests (gender * accuracy)

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.318	1	0.251
Continuity Correction	0.636	1	0.425
Likelihood Ratio	1.336	1	0.248

Annexure-A: RIFLE and AKIN criteria

AKIN criteria		Urine output	RIFLE Criteria	
Stage	Creatinine	Common to both	Class	Creatinine OR GFR
Stage 1	Increase of > or equal to 0.3 mg/dl	< 0.5 ml/kg/h for more than 6 hours	Risk	Increase in Cr × 1.5 or GFR decrease >25%
Stage 2	Increased to > 2- to 3-fold from baseline	< 0.5 ml/kg/h for> 12 hours	Injury	Increase Cr × 2 or GFR decreased >50%
Stage 3	>3-fold , or > or = 4.0 mg/dl or on RRT	< 0.3 ml/kg/h for 24 h or anuria for 12h	Failure	Cr × 3, or Cr >4 mg/dl or GFR decreased >75%
			Loss	Persistent AKI = complete loss of kidney function >4 weeks
			End Stage Renal Disease	ESRD >3 months

DISCUSSION

Acute kidney injury is a well-known serious complication affecting the hospitalized patients worldwide. It is a marker of poor prognosis and is associated with worse clinical outcome with increased mortality and morbidity. This was demonstrated by Coca SG et al in a contemporary analysis of 81 AKI patients admitted to burn units.[8] Studies have shown that early diagnosis of AKI and early intervention results in decreased mortality, morbidity and early hospital discharge.[9]

In this study we measured the accuracy of urine NGAL, a new biomarker for AKI, by comparing it with the serum creatinine in AKIN criteria. NGAL is a 20 kDa protein expressed in renal tubules which is released into the urine in case of acute or chronic kidney injury. Hence, urine NGAL level might reflect kidney injury, more specifically tissue damage. Rapid increase in urine NGAL level compared to serum creatinine level in response to AKI is one of its advantages over serum creatinine. However, serum creatinine level indicates renal function and is indirectly indicative of AKI.

Our study showed that accuracy of urine NGAL was 90.7% in diagnosing AKI in patient admitted to ICU. Most of the patients in our study were more than 40 years of age as 91 out of 97 patients in this study were above 40 years. Both the genders were equally represented in the data as 48.5% were male patients and 51.5% were female patients. There is no study done in our population previously that has measured accuracy of urine NGAL in AKI. In a study from Egypt, accuracy of NGAL was 93.3% in diagnosing AKI.[7]

Regarding the test outcomes, there were 73.2% cases that were true positive and 17.5% of cases were true negative. Only one case was false positive and there were 8.2% cases that were false negative. These false negative cases can be explained by the fact that serum creatinine is a poor marker of renal function and AKI.[10,11] As we know that creatinine levels in the serum are affected by multiple factors, most important is volume contraction, also known as prerenal AKI. In such circumstance's creatinine will rise transiently, and then return to baseline, and it may take more than 48 hours, hence it will be labelled as AKI as per AKIN criteria. In such prerenal AKI cases, urine NGAL will remain normal, as there is no renal injury, and this has been shown in different studies as well.[12–17]

Similarly, regarding the false positive results, when creatinine remained normal or increased by less than 0.3 mg/dl in 48 hours, urine NGAL came out to be positive, which is probably explained by the fact that serum creatinine increases after more than 50% damage to the kidney has been done. If the renal injury involves less than 50% of the renal parenchyma then serum creatinine will remain normal, hence this renal injury will be missed by AKIN criteria which utilizes serum creatinine as a tool to diagnose AKI. But in these circumstances urine NGAL will be increased as shown in many studies that NGAL is a marker of tubular injury and even trivial injuries to the tubular system will result in increased NGAL levels.

As far as practical application of Urine NGAL in AKI patients is concerned, with the aim of replacing or supporting classic diagnostic tools like serum creatinine or urine output, published data has revealed that NGAL testing is easy, rapid, and measurable in the lab with standard clinical platform. Moreover, it is non-invasive, and has the predictive value of detecting severity of AKI, and distinguishes prerenal azotaemia from AKI.[18] Similarly, in patients with subclinical AKI where serum creatinine-based criteria fail to diagnose, NGAL levels have been above the cut off values and described a threefold increase in risk of worst clinical outcomes like need for renal replacement therapy.[18]

The concern about cost-effectiveness of Urine NGAL was addressed and resolved by A. Parikh *et al*. They found that despite the initial higher cost of testing NGAL as compared to serum creatinine was offset by potential savings due to reduction in delayed diagnosis and treatment. Also delay in diagnosis of AKI has worse prognosis, leading to progression of the injury, with the need for renal replacement therapy and higher cost, with potential complications of severe AKI adding up to the cost. Although widespread use of NGAL for detecting AKI would result in unnecessary testing and added cost, but that too is less costly than inappropriate delays in diagnosis and treatment.[19] Overall urine NGAL seems to be much more beneficial than detection of AKI alone, the spectrum of advantages like less hospital stay, less unnecessary interventions, more patient and physician satisfaction due to overall diagnostic and prognostic benefits.

Therefore, it would be appropriate to consider and use NGAL in widespread clinical scenarios, in different patient population and age groups, in medical as well as surgical cases, both routine and acute cases. Urinary NGAL has been tested in other clinical circumstances like cardiac surgery, emergency department, operating rooms, and in other high-risk procedures such as radio contrast media injection, adult and paediatric renal and liver transplantation.[20–23] There is considerable data that shows urinary NGAL being superior then serum creatinine in detection of early and subclinical AKI, and has a better predictive value regarding dialysis requirement as well as mortality.[15]

These findings show that urine NGAL can be used as a very accurate as well as sensitive marker for AKI. Moreover, it can also diagnose AKI very early, about 24–48 hours before rise in serum creatinine. Also, it can help in identifying prerenal azotaemia, predict

outcome and the need for renal replacement therapy, and has overall cost benefit due to less hospital admission days, less unnecessary investigation and less expensive treatments. Therefore, definition of AKI may necessitate a revision with inclusion of the new biomarkers in it, and one of these biomarkers is NGAL with a high accuracy when compared to serum creatinine. Further studies are required in this field for broader application of new biomarkers like urine NGAL in diagnostic workup for AKI.

Limitations:

- It was a single centre study with participants from only one tertiary care hospital, results in other races and geographic regions may vary.
- Sample size was small, and it may not be a true representative of the large burden of AKI in critically ill patients.
- Comorbid condition such as diabetes mellitus, sepsis, and coronary artery disease were ignored in this study that may have confounded our results.

CONCLUSION

Urine NGAL is an accurate marker of AKI in critically ill patients. Therefore, it should be included in the diagnostic workup of AKI in early stages.

AUTHORS' CONTRIBUTION

MS: Literature review, Data collection, Data analysis, Data interpretation. SNM: Literature review, Conceptualization of study design. MS: Literature review, Write up, Proof reading

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