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Original Research Article

Urine neutrophil gelatinase associated lipocalin (NGAL) in septic versus non-septic acute kidney injury

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Abstract

Background: Sepsis is the most common trigger for acute kidney injury (AKI) in critically ill patients. This study is to monitor changes in urine neutrophil gelatinase- associated lipocalin (uNGAL levels between septic and non-septic AKI and also to evaluate differences between septic and non-septic AKI with uNGAL.

Material and methods: This was a prospective observational study of critically ill patients with acute kidney injury (AKI) Patients were evaluated for presenting complaints and on evaluation those who satisfied for SIRS criteria are taken up for study. In those patients with evidence of infection and positive for at least two criteria for SIRS are taken up as cases (n=30) and rest are taken as controls (n=30). All the patients were serially monitored for urine output, renal parameters, urine NGAL, APACHE II score and SOFA score. Patient urine was collected immediately after admission followed by 12, 24 and 48 hours for measuring NGAL.

Results: Mean change in NGAL (ng/ml) at 12 hour, 24 hour and 48 hour was -12.5±5, -20.5±6.74 and -29.3±10.25 respectively in septic AKI and was -0.94±6.08, -0.92±6.31 and -0.10±6.12 respectively in non septic AKI. Within group analysis showed statistically high significance ($p<0.0001$) in septic AKI but not in non septic AKI group ($P=0.97$). On evaluating between group analysis, we found significantly high difference of NGAL in septic AKI at 12 hrs, 24 hrs and 48 hrs as compared to non septic AKI ($P<0.0001$)

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Conclusion: Septic AKI patients have higher detectable urine NGAL compared with non-septic AKI patients. These differences in NGAL values in septic AKI may have diagnostic and clinical relevance as well as pathogenetic implications.

Key words

Acute kidney injury, Sepsis, Neutrophil gelatinase associated lipocalin.

Introduction

Sepsis is an important precipitant of acute kidney injury (AKI) [1]. Observational studies have found sepsis contributes to 30–50% of all AKI encountered in critically ill patients [2–6]. Septic AKI portends a poorer prognosis with lower survival when compared with AKI of non-septic origin [2, 4, 7, 8]. Yet, septic AKI may be associated with higher rates of renal recovery [3]. Considering these differences, the early identification of primarily septic from non-septic AKI may have clinical relevance and prognostic importance. Experimental studies have suggested that septic AKI may be characterized by a distinct pathophysiology that differs from ischemic/toxic-induced kidney injury [9–15]. These events may be reflected in unique patterns of plasma (p) and urine (u) biomarkers in septic AKI [16, 17]. As a consequence, the application of traditional urinary biochemical and microscopy-based tests in the early diagnosis and differentiation of AKI may be misleading in septic AKI [16–18]. Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a potentially useful diagnostic biomarker in AKI [19–21]. This study was done by hypothesizing uNGAL will differ in patients with septic compared with non-septic AKI.

Material and methods

The study protocol was approved by the Institutional Ethics Committee of Narayana Medical College, Nellore. This was a prospective observational study of critically ill patients with acute kidney injury (AKI). Patients who were admitted to ICU/HDU with a projected in-hospital stay of more than >48 hours were included in the study. Informed consent from subjects was obtained. Patients were evaluated for presenting complaints and on evaluation those who satisfied SIRS criteria are taken up for study. In those patients with evidence of infection and positive for at least two criteria for SIRS are taken up as cases (n=30) and rest are taken as controls (n=30). All the patients were serially monitored for urine output, renal parameters, urine NGAL, APACHE II score and SOFA score. Inclusion criteria were: Age >18 years; AKI (defined by fulfilling AKIN criteria) , and either sepsis (as cases) or no sepsis (as controls).

Exclusion criteria were: Prior history of kidney disease like end-stage kidney disease (K/DOQI Stage V), renal replacement therapy (RRT) prior to ICU admission, or confirmed and/or suspected acute glomerulonephritis, interstitial nephritis, renal vasculitis or obstructive etiology for AKI. Prior kidney transplant, Diabetes Mellitus, history of malignancy, history of receiving radio contrast and/or nephrotoxic drugs 48-72 hours prior to admission.

Patients were identified by daily surveillance in ICU and HDU. Patients admitted with suspected sepsis are considered eligible. Clinical data, physiological data and lab data is collected and followed up. All enrolled patients had indwelling urinary catheters. Patient urine was drawn immediately after admission followed by 12, 24 and 48 hours for measuring NGAL. Biochemical parameters (Renal function test, serum electrolytes, Arterial blood gas, cultures) were

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analyzed immediately after admission, and some tests like RFT, ABG, CUE, CBP, serum electrolytes repeated as necessary on 12, 24 and 48 hours. Urine samples for NGAL testing are collected and supernatant processed (centrifuged at 1500 rpm for 10 min) immediately. Overnight, samples are stored at -20^{0}C after processing for batched analysis. Biochemical analysis was done by Biovendor human lipocalin-2/NGAL-Sandwich ELISA. Urine NGAL was expressed as ng/ml.

Statistical Analysis

The statistical analysis was carried out with graph pad prism software Version-5, USA. Categorical data was presented as actual numbers and percentages. For normally distributed data unpaired "t" test and one-way repeated-measures analysis of variance (ANOVA) was used. Non-normally distributed data was analyzed by using non-parametric "Mann-Whitney U test". Categorical variables were analyzed with "Fischer's exact T-test". All the efficacy parameters were presented as absolute change from baseline. A negative sign indicates decrease and vice versa. For statistical significance, a two tailed *p* value of less than 0.05 was considered.

Results

In the present comparative study, out of total 60 subjects, 30 patients having septic AKI were considered as cases and 30 patients having non septic AKI were taken as controls. There were 22 males and 8 females in the Septic AKI and 20 males and 10 females in the non-septic AKI group (P=0.57). Patients Mean age was 55.2±12.3 vs 58.3±10.2 yrs in cases and control group respectively, (p=0.29). We found significantly higher APACHE II score in cases as compared to controls (24.2±6.2 vs. 18.7±8.1 respectively, p=0.004) Similarly, SOFA score was statistically significant in cases as compared to control group (8.6±2.6 vs 6.6±2.8, p=0.006). However, there was significant difference between cases and controls in patients on mechanical ventilation (p=0.27), APACHE score (p=0.004) and SOFA score (p=0.006). On evaluation of physiological parameters at baseline, we found significantly high heart rate (110±18 vs. 86±15 beats/min p<0.0001), respiratory rate (24±4 vs. 16±5 breath/min p<0.0001), temperature (101±0.5 vs. 98±0.6 0F p <0.0001), WBC count (13000±1200 vs 9500±960 mm3/ml p<0.0001) in cases as compared to control group respectively. However, there was significantly low mean arterial pressure (62.4±12.6 vs 68.3±13.6 mmHg p=0.05), Pao2/Fio2 ratio (216±90 vs. 284±84 P=0.003), Urine output (65±8 vs. 70±10 p=0.04) in cases as compared to controls. All the patients in case group and 23 patients in control group had SIRS score of more than two and was statistically significant (p=0.01) (**Table - 1**).

On further evaluation, we found that sources of sepsis in Septic AKI group was most commonly by pulmonary 9 (30%) followed by skin and soft tissue 8 (26.7%), abdomen 6 (20%), CNS 4 (13.3%) and urogenital3 (10%). On further analysis of baseline kidney characteristics, there was no significant difference in S. creatinine level (1.5±0.6 vs. 1.3±0.5 mg/dl, p=0.17), S. urea (60±12 vs 52±10 mg/dl, p=0.26) between septic AKI and non septic AKI group respectively. Similarly, on analyzing kidney characteristics after enrolment, there is no statistical significant difference in S. creatinine 1.8±0.5 vs. 1.6±0.4 mg/dl, P=0.09), S urea (96±10 vs. 92±13 mg/dl, p= 0.18) among septic AKI as compared to non septic AKI (**Table - 2**).

Among septic AKI group, 80% patients were classified as risk, 16.7% patients as Injury and 3.33% patients' failure as per AKIN criteria at baseline. After 48 hours, 63.3% were in risk category, 26.7% patients in injury and 10% patients were considered as failure. There was

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no significant change in AKIN criteria within Septic AKI after 48 hours. Similarly, among non septic AKI, 86% patients were considered as risk, 10% patients as injury and remaining 3.3% as failure at baseline. After 48 hours, 83.3% were in risk category, 13.3% patients in injury and 3.3% patients were considered as failure (**Table - 3**) (**Figure - 1**).

There was no significant change in AKIN criteria within non-septic AKI after 48 hours. There was no significant difference between groups (p=0.81). The mean change in NGAL (ng/ml) at 12 hour, 24 hour and 48 hour was 12.5±5, 20.5±6.74 and 29.3±10.25 respectively in septic AKI and was 0.94±6.08, 0.92±6.31 and 0.10±6.12 respectively in non septic AKI. Within group analysis showed statistically high significance (p<0.0001) in septic AKI but not in non septic AKI group (P=0.97) (**Table - 4**). On evaluating between group analysis, we found significantly high difference in septic AKI at 12 hours, 24 hours and 48 hours as compared to non septic AKI (P<0.0001) (**Figure - 2**).

Discussion

Acute kidney injury (AKI) is a frequent and serious complication of sepsis in intensive care unit (ICU) patients [22], particularly in the elderly [23]. Moreover, there is strong evidence that sepsis and septic shock are the most important causes of AKI in critically ill patients, account for 50% or more of cases of AKI in ICUs, and associate with a very high mortality [1]. Currently, AKI is diagnosed by measuring serum creatinine concentration, which is an unreliable and delayed marker of the deterioration of kidney function. Its rise occurs when a significant amount of renal function has been lost. Many factors are able to modify physiological levels, such as age, gender, ethnicity, dietary protein intake, muscle mass or metabolism, hydration status ,drugs and may remain within the reference range despite marked renal impairment in patients with low muscle mass [24, 25]. Creatinine, as well as blood urea nitrogen (BUN) or urine markers of kidney injury (fractional excretion of sodium, urinary concentrating ability, casts), do not directly reflect cell injury, but rather the delayed functional consequences of the damage. Due to the lack of sensitive and specific bio-markers, the identification of early stages of AKI has been impossible but, recently, neutrophil gelatinase-associated lipocalin (NGAL) is emerging as a novel biomarker for AKI from several etiologies, such as cardiac surgery, contrast nephropathy, kidney transplantation and sepsis. NGAL produced in the distal nephron increases in both serum and urine approximately 48 hours before the rise of creatinine, and shows a strong correlation with change in creatinine concentrations [26]. Urine levels of NGAL can be measured by ELISA and are a very sensitive marker of acute kidney injury, which can increase up to 1000-fold under certain conditions like post cardiac surgery [27]. An early diagnosis of AKI allows for early institution of therapeutic measures for the protection of renal function and improves the prognosis. Availability of a sensitive and specific bio-marker of AKI is particularly important in critical patients, often lacking in anamnestic data, and treated with potential nephrotoxic therapies. We conducted a prospective observational study comparing urinary NGAL in critically ill patients with septic and non-septic AKI. We found that septic AKI was associated with higher initial values of urinary NGAL, and this difference generally persisted for the study duration of 48 hours when compared with non-septic AKI. We found significant rising trends in uNGAL for septic but not for non-septic AKI groups. We found septic AKI was associated with higher peak uNGAL compared with non-septic AKI. Also, higher uNGAL showed fair discrimination for a diagnosis of septic versus non-septic AKI. We also found AKI patients with septic, when

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compared with non-septic AKI, had considerable differences across numerous clinical, physiologic and laboratory parameters. Despite similar AKI severity at enrolment, septic patients were generally older, had high APACHE II and SOFA II score. These differences have likewise been described in prior studies [2, 3, 28]. We found that septic AKI was associated with higher levels of uNGAL. One hypothesis to potentially explain this observation is that sepsis induces a greater ''injury'' to the kidney compared with other contributing factors. While higher NGAL levels have been associated with greater severity of AKI, no investigation as of yet has examined for differences in expression of NGAL by contributing factor for AKI. Alternatively, NGAL may have higher expression in inflammatory states such as sepsis or in selected malignancies. Indeed, Wheeler, et al. found higher values of pNGAL in children with septic shock compared to those with either SIRS or healthy controls [24]. NGAL is constitutively expressed in several tissues including lung, NGAL expression has been found to be significantly up-regulated in several forms of cancer [25, 29, 30]. Likewise, NGAL expression has been found to be increased during acute inflammatory and/or infectious processes [25, 29, 31]. These observations suggest NGAL may represent an emerging global biomarker for inflammation, tissue injury, illness severity and organ failure, and correlate with survival in sepsis. However, the study conducted by Nickolas, et al. [21] did not find superiority of NGAL level over serum creatinine level predicting subsequent AKI in patients admitted to an emergency department given that patients already with AKI and those with subclinical AKI were included. As a future prospective, levels of exosomal transcription factors may also be used to identify AKI [32].

Study limitations

There are limitations to our study, critically ill patients are often exposed to numerous concurrent sources for kidney injury. Accordingly, as noted, there were differences between groups in exposure to aminoglycosides and other nephrotoxic drugs. Similarly, the old aged septic AKI patients have a higher prevalence of cancer, which may impact the observed differences in NGAL between septic and non-septic groups. In addition, we did not include a septic non-AKI control group for comparison. Therefore, our data are not able to discriminate the ability of uNGAL for the early diagnosis of AKI per se. Future investigations of novel AKI biomarkers, such as NGAL, should continue to explore whether there is differential expression across AKI syndromes, evaluate the potential role of NGAL in therapeutic monitoring in response to interventions, their role during weaning from renal support and their association with renal recovery and/or progression to chronic kidney disease.

Conclusion

In summary, Septic AKI patients have higher detectable urine NGAL compared with non-septic AKI patients. These differences in NGAL values in septic AKI may have diagnostic and clinical relevance as well as pathogenetic implications. Larger comparative studies are required for further evaluation.

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Table – 1: Baseline demographic and baseline physiological characteristics.

Parameters	Septic AKI N=30	Non-Septic AKI N=30	*p* Value
Gender (M/F)	22/8	20/10	0.57
Age (years)	58.3±10.2	55.2±12.3	0.29
APACHE II score	24.2±6.2	18.7±8.1	0.004
SOFA II score	8.6±2.6	6.6±2.8	0.006
Mechanical ventilation	12 (40%)	8 (26.7%)	0.27
Heart rate	110±18	86±15	<0.0001
Respiratory rate	24±4	16±5	<0.0001
Temperature	101±0.5	98±0.6	<0.0001
Mean arterial pressure	61.4±12.6	68.3±13.6	0.04
>2 SIRS (%)	100	76.7	0.01
Pao2/Fio2 ratio	216±90	284±84	0.003
WBC count(mm3/)	13000±1200	9500±960	<0.0001
Urine output(ml/hr)	65±8	70±10	0.04

Table – 2: Summary of kidney function at enrolment and clinical outcomes.

Parameters	Septic AKI N=30	Non-Septic AKI N=30	*p* Value
Baseline Kidney characteristics			
S. Creatinine	1.5±0.6	1.3±0.5	0.17
S. Urea	60±12	52±10	0.26
Enrollment Kidney characteristics			
S. Creatinine	1.8±0.5	1.6±0.4	0.09
S. Urea	96±10	92±13	0.18

Table – 3: AKI Progression (AKIN criteria).

Stages	Septic AKI			Non-Septic AKI		
	Baseline	After 48 hours	*p* value	Baseline	After 48 hours	*p* value
Risk	24 (80%)	19 (63.3%)	0.17	26 (86.7%)	25 (83.3%)	0.78
Injury	5 (16.7%)	8 (26.7%)		3 (10%)	4 (13.3%)	
Failure	1 (3.33%)	3 (10%)		1 (3.33%)	1 (3.33%)	

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Table – 4: Mean change in NGAL from baseline.

NGAL (ng/ml)	At 12 hours	At 24 hours	At 48 hours	P value (Within group)
Septic AKI	12.5±5	20.5±6.74	29.3±10.25	<0.0001
Non septic AKI	0.94±6.08	0.92±6.31	0.10±6.12	0.97
P value (between group)	< 0.0001	< 0.0001	< 0.0001	

Figure – 1: AKI progression in cases and controls.

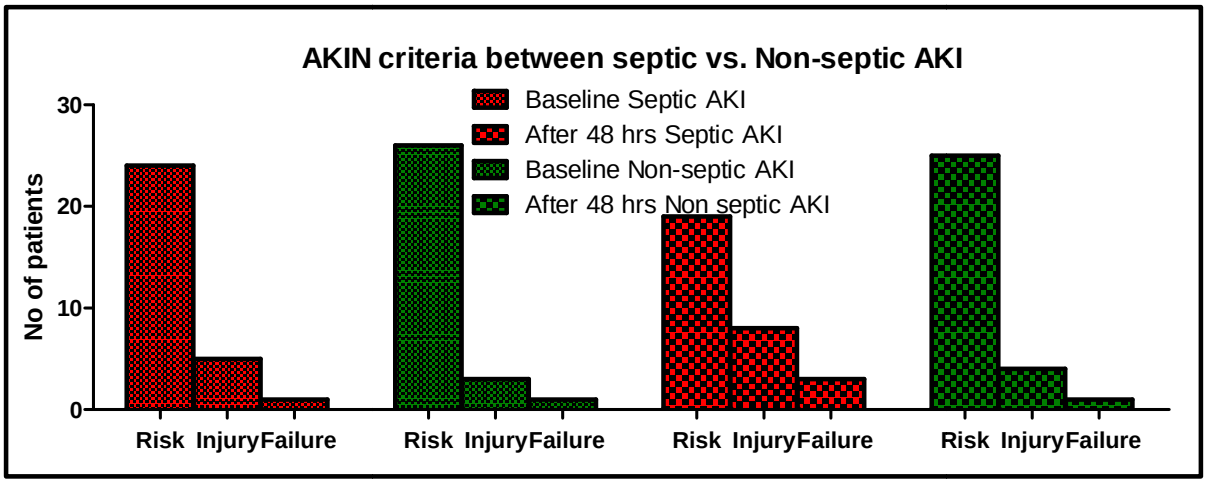
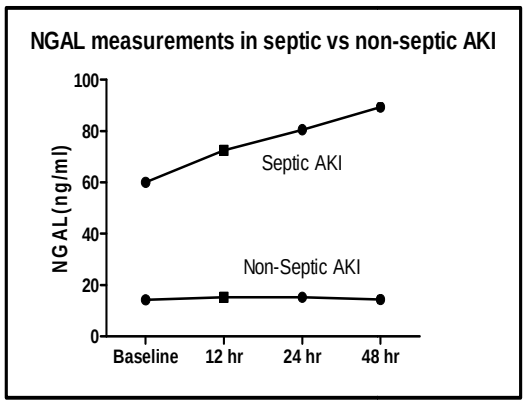
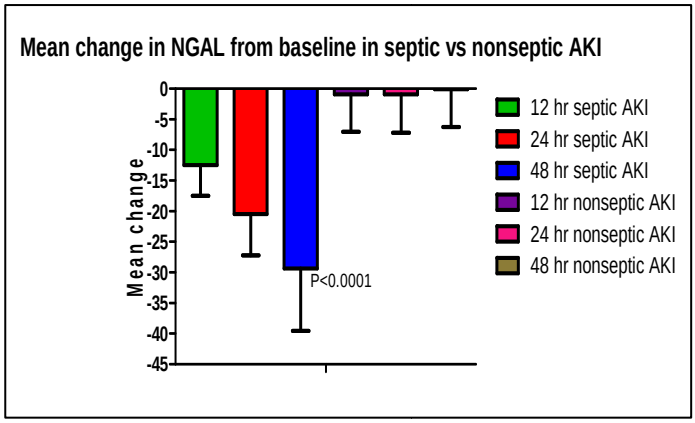


Figure – 2: NGAL Measurements in septic vs Non-septic AKI and Mean change in NGAL from baseline in Septic vs Non-septic AKI.





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