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Panacea Journal of Medical Sciences

Journal homepage: www.ipinnovative.com

Original Research Article

Utility of urine microscopy and urinary biomarkers in early detection of acute kidney injury in a cohort of patients admitted with a clinical diagnosis of acute decompensated heart failure

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ARTICLE INFO

Article history:
Received 24-08-2020
Accepted 06-09-2020
Available online 29-12-2020

Keywords:
Acute Kidney Injury (AKI)

ABSTRACT

Background: Acute Kidney Injury (AKI) is a common clinical syndrome in hospitalized patients, especially in intensive care units and is a strong risk factor for development of Chronic Kidney Disease (CKD). AKI is a common association in patients admitted for Acute Decompensated Heart Failure (ADHF). AKI is an independent predictor of mortality and poor long term outcome in patients presenting with ADHF. Presently available diagnostic tests in particular serum creatinine, are not helpful in early detection of AKI. Thus a diagnostic tool which can help in early detection of AKI, differentiate various types of AKI, grade the severity of AKI, and suggest appropriate management strategy in patients with ADHF, is need of the hour.

Objectives: To analyze role of urine microscopy & urinary biomarkers (N-Acetyl-beta-D-Glucosaminidase, NAG; and Kidney injury molecule type 1, KIM-1) in early detection of AKI and its differentiation into pre-renal and ATN variety in patients admitted with a clinical diagnosis of ADHF.

Materials and Methods: 40 patients of ADHF with AKI, along with 25 controls (ADHF without AKI) were studied from January 2019 to December 2019. Urine microscopy with sediment analysis and measurement of urinary biomarkers were done.

Results: Urine microscopy helped in differentiation of pre-renal AKI from ATN. The role of urinary sediment examination in risk stratification of AKI did not show a significant correlation between presence of granular casts and three stages of AKI with a P value of 0.561. Levels of urinary KIM-1 and NAG were higher in ADHF with AKI cases as compared to controls with a significant P value of <0.0001 for KIM-1 and 0.003 for NAG. Levels were also higher in cases whose samples were taken within 24 hours of symptom onset of AKI, with a highly significant p value of <0.0001 and 0.001 for KIM-1 and NAG respectively. However urinary biomarker levels did not help in risk stratification of the patients. The correlation of three stages of AKI with urinary levels of KIM-1 and NAG had a P Value of 0.74 and 0.504 respectively.

ROC of NAG and KIM-1 were plotted. AUC calculated for KIM-1 was 0.998, for NAG was 0.718 and for the combination was 0.724. There was a significant difference between AUC of KIM-1 and NAG with a p value of <0.001. There was also a significant difference between AUC of KIM-1 and combination of KIM-1 and NAG with a p value <0.001.

Conclusions: Urine microscopy is a readily available & inexpensive tool which can help in differential diagnosis of AKI into pre-renal AKI and ATN variety; so that correct therapy can be initiated in time but may not always help to risk stratify patients. The two urinary biomarkers analyzed (KIM-1 and NAG) are useful in early detection of AKI in ADHF patients, however their combination did not have any added advantage of early diagnosis.

https://doi.org/10.18231/j.pjms.2020.050

1. Introduction

Heart failure (HF) is a growing problem worldwide. The incidence of hospitalizations ADHF has increased, likely consequential to the aging population, improved survival after myocardial infarction, and prolonged survival of HF patients with current medical and device therapies.[1]

ADHF is a syndrome, defined as the sudden or gradual onset of the signs or symptoms of heart failure requiring unplanned office visits, emergency room visits, or hospitalization. Regardless of the underlying precipitant of the exacerbation, pulmonary and systemic congestion due to increased left- and right-heart filling pressures is a nearly universal finding in ADHF.[2] ADHF is usually a clinical diagnosis based on focused history and physical examination. Investigations such as electrocardiogram, chest X-ray, 2D echo and NT pro BNP levels are used for further confirmation.

AKI is characterized by a sudden (hours to days) impairment of kidney function. Thus AKI is a clinical syndrome characterized by a rapid reduction in renal excretory function caused by a variety of factors. Various studies point to a rising incidence of AKI in critical care settings, especially in patients admitted with a clinical diagnosis of ADHF. There has been some improvement in outcomes over time, however the mortality associated with AKI remains unacceptably high.

Evidence-based clinical practice guidelines for AKI have been hampered by the many different definitions used in the literature. To address this issue an independent collaborative network of international experts established the Acute Kidney Injury Network (AKIN). The AKIN included representatives from the Acute Dialysis Quality Initiative (ADQI) group which previously devised the RIFLE staging system for AKI.[3] AKIN proposed that the term AKI represents the entire spectrum of acute renal failure.[4] They also proposed the uniform standards for diagnosing and staging AKI (modified from the RIFLE staging system).

AKI is common in patients admitted for ADHF with prevalence upto 20%. It is recognised that AKI is a independent predictor of both in hospital and 1 year mortality.[5]

The heart and kidney are very closely related. Thus derangement of cardiac function can lead to renal dysfunction, recently referred to as "cardiorenal syndrome (CRS)" or inversely as "renocardiac syndrome". In 2008, Ronco et al.[6] classified CRS into 5 subtypes, By this classification, type 1 CRS is the development of renal dysfunction in clinical situation of ADHF.

Coexistence of acute cardiac and renal dysfunction, termed as acute CRS has been shown to correlate with increased mortality and all manner of adverse outcomes,[7] and may increase the risk of subsequent development of CKD.[8]

Although most patients who develop acute CRS experience a mild form of AKI (e.g., Kidney Disease Improving Global Outcomes [KDIGO] or Acute Kidney Injury Network [AKIN] stage 1 or RIFLE R) and do not progress to more severe AKI (KDIGO/AKIN stage 2/3 or RIFLE F) or require dialysis, approximately 29%-48% of these patients progress to a higher stage of AKI.[9,10]

Recent studies have demonstrated that risk of mortality exponentially increased with increasing stages of AKI in the setting of ADHF.[11]

Early detection of patients at higher risk for AKI progression would help physicians to plan and initiate the appropriate managements to improve renal safety of therapies, augment surveillance of cardiac and renal dysfunction, and develop renal-preserving treatments.[12]

Unfortunately, predicting which patients with CRS will suffer progressive AKI or proceed to death is clinically challenging. In patients with ADHF, fluid retention, low protein intake, and decreased creatinine production secondary to muscle atrophy may dissociate creatinine levels from reflecting the true severity of renal dysfunction. Diagnostic mainstays such as the fractional excretion of sodium and urea have been shown to be suboptimal in a variety of clinical settings.[13]

Assessment of serum creatinine is a relatively insensitive measure for early detection of AKI. Assessment of various biomarkers for renal tubular injury (e.g., neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule-1 [KIM-1], IL-18 and N acetyl D glucosamine (NAG) offers early detection of AKI and prognostic information in multiple clinical settings such as cardiac surgery, ICU, transplantation, and cirrhosis.[14] However, their utility has not been tested in ADHF.

Urine microscopy is the oldest and one of the most commonly used tests for differential diagnosis of AKI. It can provide the vital information to differentiate AKI into traditional categories of pre-renal azotemia and acute tubular necrosis (ATN). Therapies and prognosis for pre-renal AKI and ATN differ substantially; therefore, early clinical diagnosis and differentiation is important. Urine microscopy with sediment examination is commonly suggested for patients with AKI in the literature, but its precise diagnostic value is not clearly known and further clinical trials are required.

Thus an ideal biomarker for AKI is required which would help clinicians and scientists in early detection of AKI in hospitalized patients with ADHF. The aim of this study was to identify role of urine microscopy and urinary biomarkers (KIM1, NAG) in early detection of AKI in patients admitted in critical care unit with a clinical diagnosis of ADHF.

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2. Materials and Methods

Urinary soluble KIM-1 protein was quantified by a enzyme-linked immunosorbent assay system (ELISA method). First the 96-well microplate is coated with 100 mL per well of the diluted Capture Antibody against KIM-1 and the plate is sealed and incubated overnight at room temperature. Each well is aspirated and washed with wash buffer for a total of 3 times. Plates are then blocked by adding reagent diluents to each well and incubated at room temperature. Aspiration/Wash step is repeated before adding the sample. Plates are again incubated, washed and then a detection antibody is added. After this streptavidin-HRP, substrate solution and stop solution are added in similar steps. Finally the optical density of each well is determined immediately, using a microplate reader set to 450 nm and a wavelength correction is done. Results were obtained by creating a standard curve by reducing the data using computer software capable of generating a four parameter logistic (4-PL) curve-fit.

Urinary NAG (N-Acetyl-beta-D-Glucosaminidase) was measured by colorimetric assay using a commercially available kit. (Diazyme Laboratories, Poway, CA92064, USA). Three reagents, a calibrator and a control were used. The product formation is detected by the development of color at 505nm by absorbance reading at this wavelength. Urinary NAG was calculated in the units of IU/L as per the given formula.

3. Results

Out of 18 patients with a final diagnosis of pre-renal AKI only 1 patient had granular cast in urine, while those with ATN, 15 out of 22 (68.2%) had granular casts. Similarly 50% of the pre-renal patients had hyaline casts in urine as opposed to only 1 patient in ATN variety (4.5%). Results had a highly significant p value of <0.0001. Thus urine microscopic examination with analysis of sediments was a useful diagnostic test to differentiate pre-renal azotemia from ATN.

Table 1: Correlationof final diagnosis with presence of urinary casts

Final Diagnosis	Casts		
	Nil N (%)	Hyaline N (%)	Granular N (%)
Prerenal (N=18)	8(44.4%)	9(50%)	1(5.6%)
ATN (N=22)	6(27.3%)	1(4.5%)	15(68.2%)
Total (N=40)	14(35.0%)	10(25%)	16(40%)

The role of urinary sediment examination in risk stratification of AKI did not show a significant correlation between presence of granular casts and 3 stages of AKI with a P value of 0.561.

Table 2: Correlation of stages of AKI with presence of urinary casts

Akin Stage	Casts		
	Nil N (%)	Hyaline N (%)	Granular N (%)
1(N= 9)	3 (33.3%)	3 (33.3%)	3 (33.3%)
2(N=12)	5 (41.7%)	4 (33.3%)	3 (25.0%)
3(N=19)	6 (31.6%)	3 (15.8%)	10 (52.6%)
Total (40)	14 (35%)	10 (25%)	16 (40%)

Table 3: Urinary biomarker analysis in diagnosing AKI in ADHF

Variable	AKI (N=40)	Control (N=25)	P value
KIM-1(μg/dl)	1.56±0.42	0.46±0.19	**<0.0001**
NAG (IU/L)	142.87±160.3	51.96±54.57	**0.003**

Levels of urinay KIM-1 and NAG were higher in AKI cases as compared to controls with a significant P value of <0.0001 for KIM-1 and 0.003 for NAG.

Table 4: Urinary biomarker analysis in early detection of AKI in ADHF

Variable	AKI* (N=22)	Control (N=25)	P value	Z
KIM-1	1.5	0.45	<0.0001	5.863
NAG	100.60	23.52	0.001	3.283

* AKI cases were those in which urine samples were taken within 24 hours of symptom onset.

Levels were also higher in cases whose samples were taken within 24 hours of symptom onset of AKI, with a highly significant p value of <0.0001 and 0.001 for KIM-1 and NAG respectively. However urinary biomarker levels did not help in risk stratification of the patients.

4. Discussion

AKI is a well recognized complication in almost 25 to 30% patients hospitalized with ADHF, and it is associated with increased morbidity and mortality.[15] In Kor-HF registry, worsening of renal function, defined as increasing serum creatinine levels more than 1.5 times baseline, happened in 21.5% of AHF patients.[16] Although there is no concrete criteria, worsening renal function is often defined as an increase in sCr $\geq$0.3 mg/dL from baseline value.

Evaluation of AKI using conventional biomarkers like serum creatinine (sCR) has many limitations. Serum creatinine is largely influenced by age, gender and muscle mass. Also it is relatively insensitive in early detection of AKI because of its slow kinetics. Hence marked reduction in eGFR may cause relatively small changes in sCr levels in the early stage of acute kidney injury (24-48 hours). In addition, sCr kinetics are dependent on baseline renal function so that the time interval from kidney injury to 50%

increase in sCr ranges from 4 hours with normal baseline renal function to more than 1 day with underlying advanced renal dysfunction.[17] More importantly, sCr level is a marker of renal function rather than kidney injury, so, increased sCr levels are not always representative of kidney injury. Hence there was a need of ideal biomarker which can help in early detection of AKI in ADHF setting, differenciate pre-renal AKI from ATN and suggest appropriate treatment stratigies.

The most common cause of AKI in hospitalized patients is ATN followed by pre-renal AKI. Urine microscopy is a valuable diagnostic tool which can help to differentiate these two varieties of AKI. The main objective of this study was to describe the role of urine microscopy and novel urinary biomarkers in early diagnosis of AKI and in differentiating between pre-renal and renal AKI. This early differential diagnosis of AKI would assist in taking precautions to avoid further renal injury and potentially initiate early treatment to prevent kidney failure. Also, it would avoid worsening of the clinical course with incorrect therapies. For example, rapid-volume resuscitation in patients with pre-renal AKI as a result of true volume depletion or judicious intravenous fluid use in patients with ATN would be appropriate management approaches guided by early diagnosis. Acute kidney injury was diagnosed in cases on the basis of clinical history, medical records and as per definition of AKI given by AKIN. In many cases urine output criteria was used to diagnose AKI in view of non-availability of baseline serum creatinine values.

5. Conclusion

Recent studies have shown a rising trend in the incidence of AKI especially in hospitalized patients with ADHF. AKI is an independent predictor of increased short term and long term morality in ADHF patients. AKI also increases the risk of developing CKD in long run. Thus diagnosing AKI early and treating it adequately is essential to prevent development of end stage renal disease and improve outcomes in ADHF patients.

Urine microscopy is a readily available, rapid and inexpensive tool which can provide vital information for differential diagnosis AKI so that correct therapy can be initiated in time. Serum creatinine used through centuries to monitor renal function is insensitive in early detection of AKI and lags behind changes in GFR by days. A number of studies have been done to study the role of urine microscopy and urinary biomarkers to accomplish above mentioned goal. Also a penal of urinary biomarkers have been used to improve the diagnostic performance of the test.

This study clarifies the utility of urine microscopy as a very basic and informative test to identify patients with severe variety of AKI i.e. ATN. The two urinary biomarkers analyzed in this study (KIM-1 and NAG) have been found to be useful in early detection of AKI in ADHF; however their combination did not have any added advantage.

6. Source of Funding

No financial support was received for the work within this manuscript.

7. Conflict of Interest

The authors declare they have no conflict of interest.

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Cite this article: Goyal P, Verma R, Sharma SS, Ganiger VC, PG. Utility of urine microscopy and urinary biomarkers in early detection of acute kidney injury in a cohort of patients admitted with a clinical diagnosis of acute decompensated heart failure. *Panacea J Med Sci* 2020;10(3):240-244.