ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 7, Issue – 4, August – 2022 , Page No. : 19 – 23

Is urinary activin A- a Novel biomarker for acute kidney injury- a prospective cohort

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Citation this Article: Dr. J.N. Ambika Bai, Dr. Syeda Sobia Harmain, Dr. B Rajini, Dr. Mujahid Mohammed, Dr. Shobha Mohammed, "Is urinary activin A- a Novel biomarker for acute kidney injury- a prospective cohort", IJMSIR- August - 2022, Vol – 7, Issue - 4, P. No. 19 – 23.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Activin-A is a cytokine belonging to the TGF β superfamily (Transforming Growth Factor) that regulates the growth and differentiation of cells in various tissues normally absent in normal kidneys and it significantly increased in Ischemic kidney, tubular regeneration after renal ischemia. In the current research study, we measured urinary activin-A along with Neutrophil Gelatinase associate lipocalin (NGAL) urinary levels and serum creatinine levels in acute kidney injury (AKI) caused due to hypotension, sepsis, drug-induced, and contrast-induced nephropathy (CIN) and Miscellaneous causes. In this analysis, we measured urinary activin-A levels and compared them with urinary NGAL levels in AKI patients (n=50), along with the serum creatinine levels, statistical analysis releveled Estimation of urinary Activin-A showed an increase in all the group's miscellaneous group 57±26 (95% CI 42-73), in hypotension group 113±10 (95% CI 102-124), in the sepsis group 235±104 (95% CI 160- 310), in the CIN group 176±80 (95% CI 119-233) and in the drug-induced group 133±35 (95% CI 108-158), with a p= 0.0001 and F=13.06 and statistically significant between the groups. urinary activin-A is a better non-invasive marker for identifying the progression of AKI to CKD.

Keywords: Activin-A, AKI, CKD, NGAL, Serum Creatinine and Urinary biomarker.

Introduction

In clinical settings, acute kidney injury (AKI) is a critical and potential devasting condition and has many pathological features such as tubular injury and change in GFR. Approximately 13.3 million people are affected by

AKI in the world. The incidence of mortality and morbidity is increasing day by day globally due to AKI, which has multiple cofounders. Conventional biomarker serum creatinine is a useful biomarker of renal function but its elevation in serum is questionable. The increase of serum creatinine occurs when considerable damage has occurred to the kidney [1]. Several novel biomarkers both serum and urinary, such as urinary neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule -1 (KIM-1) and cystatin C were made their presence in detecting acute kidney injury early in recent years so that the therapeutic interventions can be adopted to stop the for further damage of kidney [2]. KIM-1 has not only to be a diagnostic biomarker it is prognostic. Recently novel biomarkers like insulin growth factor binding protein 7 (IGFBP-7) and tissue inhibitor of metalloproteinase 2 (TIMP-2) have been used to predict the onset of severe AKI with significantly greater accuracy in detecting AKI [3]. However clinical biomarkers reflecting the pathophysiological phase of AKI are still lacking. Due to these lacunae, we tried to explore and analyse the levels of urinary Activin-A in AKI patients. Activin-A is one of the transforming growth factor (TGF) β-superfamily and is an essential factor in renal organogenesis. Organ cultures showed that activin-A inhibits the branching morphogenesis of uretic buds [4]. as well as ureteric bud budding from the Wolffian duct [5]. Animal experiments on mice showed overexpressing of truncated type II activin receptors, and the number of glomeruli increased significantly [6]. In one of the invitro tubulogenesis models using Madin-Darby canine kidney (MDCK) cells, activin-A was significantly inhibited, but in contrast an antagonist of activin-A, follistatin induced branching tubulogenesis [7]. This research suggests that activin-A negatively regulates branching morphogenesis during kidney organogenesis. Researchers previously reported the absence of activin-A in the normal kidney, which appears in ischemic renal tubular degeneration in albino rats [8]. Studies on mice showed a significant increase of serum activin-A in renal ischemia and undetectable in urine [9]. In the current study, we tried to fill the lacunae by estimating urinary activin-A levels in AKI patients with another urinary biomarker NGAL.

Materials and methods: The current study includes 50 patients with AKI, treated at a tertiary health care centre attached to Mamata Academy of Medical Sciences, Hyderabad, Telangana, from December 2021 to May 2022. AKI was diagnosed and staged for severity according to kidney disease improving global outcomes (KDIGO) guidelines. 29. Patients suffering from existing renal insufficiency whose eGFR was 45mL/ min/1.73^2 before the onset of AKI, Corona positive, hypertensive and diabetics were excluded from the study. Patients classified as AKI under KIDGO criteria were enrolled for the study. Inform consent from all the study participants was obtained by using a standard informed consent form. The study was approved by the human institutional ethical committee and Good Laboratory Practice (GLP) was followed during experimentation.

Sample and data collection: Data such as age and gender physical parameters (height and weight) of the patients were extracted from the clinical sheets serum and urine samples were collected from the study participants and stored at -40^{o}C for further analysis. Urinary and serum Activin-A (DAC00B), and urinary NGAL (DLCN 20) were measured by using ELISA kit make (China), accessed on automated CLIA -CL900i (Mindray).

Statistical analysis

Obtained data were calculated by using GraphPad Prism version 9.4.0 (USA), Descriptive statistics and ANOVA

Tukey's multiple comparisons were done to prove the significance level at p<0.05 at 80% power of the study, with a 95% confidence interval. The sampling method used was convenient sampling as the frequency of cases was less, and care was taken to enrol the patients.

Results

Twenty-five patients with AKI were males and the rest of them were females. Of the enrolled patients were 14 with miscellaneous causes, 6 were suffering from hypotension, 10 were from sepsis, 10 were with CIN and the remaining 10 patients were drug-induced. Serum creatinine, urinary NGAL and urinary Activin-A levels were estimated and correlated for their early rise with serum creatinine levels. Serum creatinine levels were measured to prove the relationship between urinary parameters Activin-A and NGAL and their early appearance in urine. Our data suggest that in patients with serve sepsis there was an increase in serum creatinine levels 2.6 ± 0.58 (95% CI 2.2-3.0), in the group of Hypotension 2.9±0.48 (95% CI 2.4-3.4), in the miscellaneous group 2.0±0.77 (95% CI 1.5-2.4), in the CIN group 1.8±0.65 (95% CI 1.4-2.3), in the group drug-induced 1.8±0.66 (95% CI 1.3-2.2) Figure1,6. ANOVA with Tukey's multiple comparisons showed a significant relationship between the different groups with p=0.02 and F= 4.74. Estimation of urinary Activin-A showed an increase in all the group's miscellaneous group 57±26 (95% CI 42-73), in hypotension group 113±10 (95% CI 102-124), in the sepsis group 235±104 (95% CI 160-310), in the CIN group 176±80 (95% CI 119-233) and in the drug-induced group 133±35 (95% CI 108-158), with a p= 0.0001 and F=13.06 and statistically significant between the groups. Estimation of NGAL showed in the miscellaneous group 583±107 (95% CI 521- 645), in hypotension group 643±28 (95% CI 614-673), in the sepsis group 924±53 (95% CI 886-962), in CIN group 798±90 (95% CI 734-862), and in drug-induced group 524±135 (95% CI 428-620) with a p<0.0001, F=30.27 in between the groups. The correlation of Activin A and NGAL suggests a statistical significance between the groups P<0.0001, F 151.3, and *** statistically significant Figure 5, and the correlation and correlation of creatinine and urinary NGAL, Activin-A revealed P<0.0001, F 151 and *** statistically significant. Figures 1-6.

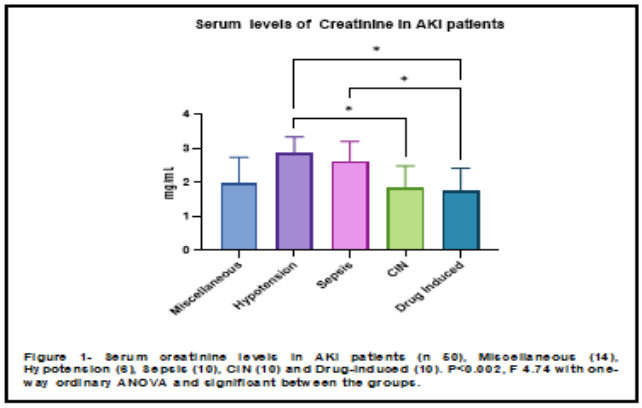

Figure 1- Serum creatinine levels in AKI patients (n 50), Miscellaneous (14), Hypotension (8), Sepsis (10), CIN (10) and Drug-induced (10). P<0.002, F 4.74 with one-way ordinary ANOVA and significant between the groups.

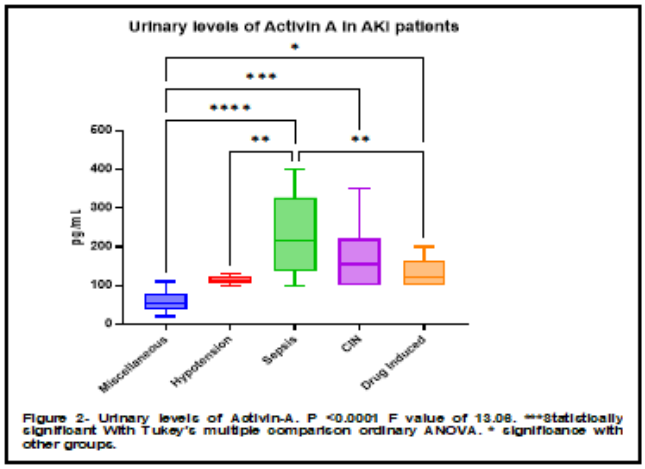

Figure 2- Urinary levels of Activin-A. P <0.0001 F value of 13.06. ***Statistically significant With Tukey's multiple comparison ordinary ANOVA. * significance with other groups.

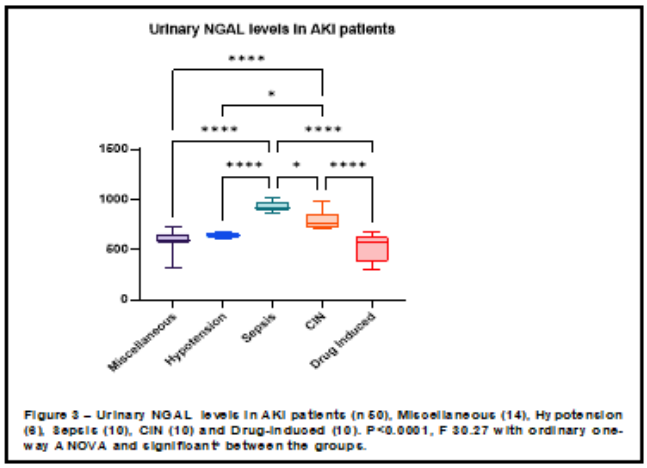

Figure 3 – Urinary NGAL levels in AKI patients (n 50), Miscellaneous (14), Hypotension (8), Sepsis (10), CIN (10) and Drug-induced (10). P<0.0001, F 30.27 with ordinary one-way ANOVA and significant between the groups.

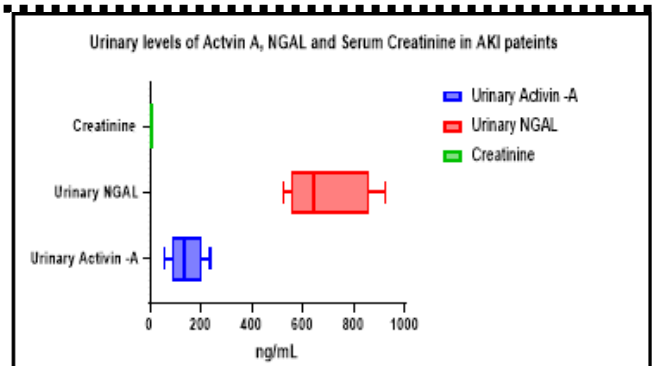

Figure 4- Urinary Activin A, Urinary NGAL and serum Creatinine levels in AKI patients (n=50), Miscellaneous (14), Hypotension (06), Sepsis (10), CIN (10) and Drug-Induced (10). Data presented as Mean±SEM, P<0.0001, F 238.5 fixed effects type III *** statistically significant.

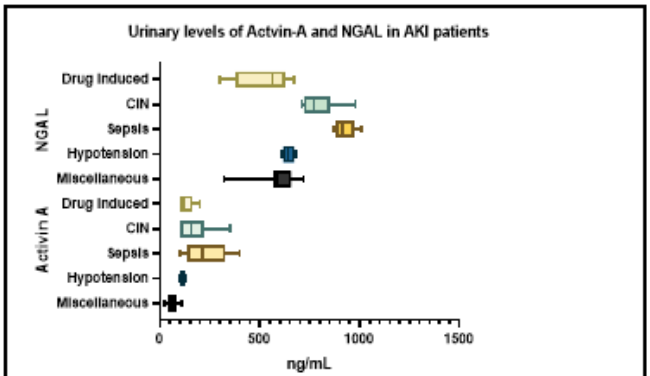

Figure 5- Urinary Activin A, Urinary NGAL levels in AKI patients (n=50), Miscellaneous (14), Hypotension (06), Sepsis (10), CIN (10) and Drug-Induced (10). P<0.0001, F 151.3, *** statistically significant.

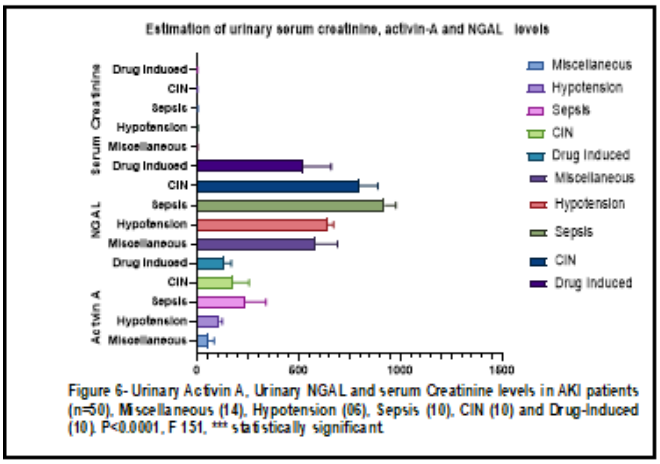

Figure 6- Urinary Activin A, Urinary NGAL and serum Creatinine levels in AKI patients (n=50), Miscellaneous (14), Hypotension (06), Sepsis (10), CIN (10) and Drug-Induced (10). P<0.0001, F 151, *** statistically significant

Discussion

Activin-A is a cytokine belonging to the TGF β superfamily (Transforming Growth Factor) that regulates the growth and differentiation of cells in various tissues normally absent in normal kidneys and it significantly increased in Ischemic kidney, tubular regeneration after renal ischemia. Previous data on animal studies showed renal ischemia suggests the increase of Activin-A may be due to renal tubular damage. In the same study, the authors declared that the beta-A subunit of mRNA for Activin-A and activin-A protein are absent, furthermore, levels of activin-A significantly correlated with renal ischemia [10]. In the current study, we found supporting evidence that there was an increase in urinary Activin-A levels in AKI patients. Urinary activin levels were significantly higher in patients with sepsis which is 3 stage of AKI when compared to other conditions such as hypotension, miscellaneous, drug-induced and CIN. The increase of urinary activin-A is positively correlated with the increased levels of NGAL. NGAL (Neutrophil gelatinase - associated lipo calin increase was demonstrated in a previous animal study [11], and the same correlates with our findings. The current study demonstrated the increase of urinary activin-A levels way before the increase of NGAL. Activin-A not only suppresses tubular proliferation but also promotes renal fibrosis. Activin-A is a potent activator of renal interstitial fibroblasts [12]. Ardently high levels of urinary activin A might be a trigger leading to the transition of AKI to CKD. In the present study, changes in renal functions were observed in patients with various causes of AKI. Administration of recombinant follistatin an endogenous activin antagonist reduced the fibrotic area in rats [13]. Sotatercept a ligand trap to the activin-A type II receptors decreased renal fibrosis and proteinuria [14]. Our findings suggest an increase in urinary activin-A which supports the earlier studies.

Conclusion

Urinary Activin-A may be used as one of the novel biomarkers which can detect AKI and its progression to CKD early when compared to other novel biomarkers, hence clinicians can adopt the biochemical screening of urinary Activin-A in kidney-related disorders as it is non-invasive. However, our study had some limitations such

as less sample size and a one-centre study, more studies are warranted with cluster-based sampling with a larger sample size.

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