SUBCLINICAL AND CLINICAL CONTRAST-INDUCED ACUTE KIDNEY INJURY: RESULTS FROM THE ENCINO STUDY (NCT 00693329)

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Abstract

Background: NGAL is an early biomarker for acute kidney injury. Contrast-induced acute kidney injury (CI-AKI) is associated with adverse outcomes in CKD patients. We sought to characterize blood NGAL level and the degree of kidney injury reflected by further increases in NGAL of CKD patients who underwent cardiac catheterization.

Methods: This study was a prospective, blinded assessment of blood samples from patients with eGFR between 15 and 90 ml/min/1.73 m2 undergoing elective coronary angiography with iodinated contrast. We excluded renal transplant recipients, dialysis patients and prior exposure of contrast within 30 days. Blood NGAL was measured using the Alere assay and serum creatinine was measured using isotope dilution mass spectrometry traceable methods. Samples were obtained at baseline, 1, 2, 4, 6, 12, 24, and 48 hours after contrast administration.

Results: A total of 63 subjects were enrolled with a mean age of 69.43±9.32 years and a mean eGFR of 48.17±16.45 ml/min/1.73 m2. There was a graded increase in baseline NGAL levels across worsening stages of CKD. Eight patients were diagnosed with CI-AKI by diagnostic criteria of 2012 Kidney Disease International Global Outcomes (KDIGO) definition of CI-AKI, and 7 developed subclinical CI-AKI defined by a twofold or greater rise in NGAL. Two subjects met both creatinine and NGAL criteria. Binary logistic regression found no relationship between baseline eGFR or diabetes on the composite outcome (clinical and subclinical AKI).

Conclusion: Baseline and post-procedure NGAL are progressively elevated according to the baseline stage of CKD. Using a twofold rise in NGAL, 46.7% of composite CI-AKI is detected and complements the 53.3% of cases identified using KDIGO criteria. Traditional risk predictors (eGFR and diabetes) were not independently associated with composite outcome.

Methods

The ENCINO (Neutrophil Gelatinase-Associated lipocalin (NGAL): A Novel Blood Marker for Determining the Risk of Developing Contrast-Induced Nephropathy) study was a prospective, blinded, cohort study performed at three centers in Michigan *(clinicaltrials.gov: NCT 00693329)*. Subjects over age 18 who were undergoing non-urgent coronary angiography with the intent of ad hoc PCI were screened and eligible if the eGFR calculated by the four-variable MDRD equation was less than 90 ml/min/1.73 m^2. Subjects were excluded if they were renal transplant recipients, treated with maintenance hemodialysis, or if they had received intravascular contrast within the preceding 30 days. Blood specimens were obtained at baseline, 1, 2, 4, 6, 12, 24, and 48 hours after contrast administration. The baseline plasma Cr and all follow-up values were measured by a core laboratory using isotope dilution mass spectrometry traceable methods, which may not have been the same methods used for screening at the local sites. NGAL was measured in EDTA-anticoagulated plasma using the extended range Alere™ Triage® NGAL immunoassay. This assay has a measurable range of 15 to 1300 ng/mL with a CV of 13.9% using the replicate values from 51 samples with a mean concentration of 400.0 ±100.0 ng/ml. NGAL and Cr results were not revealed to investigators or participants during the study. Clinical CI-AKI was defined by criteria of 2012 the Kidney Disease Improving Global Outcomes (KDIGO)'s guidelines on AKI; (1) increase in serum Cr by ≥ 0.3 mg/dl (≥26.5 μmol/l) within 48 hours, or (2) increase in serum Cr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or (3) urine volume <0.5 ml/kg/h for 6 hours. "Subclinical AKI" was defined as increase in blood NGAL equal or more than 2 times of baseline without serum Cr change that met criteria of AKI by 2012 KDIGO guideline. Univariate statistics were reported in counts and proportions and means ± SD as appropriate. The Kolmogorov-Smirnov was used to test for test for normality of the baseline NGAL distribution before use of parametric statistics. One-way ANOVA was used to compare means of continuous variables stratified into stages of CKD according to the eGFR. Binary logistic regression was used to evaluate eGFR and diabetes forced into the model as predictors of the composite outcome of subclinical plus clinical AKI. Wilcoxon signed rank test was applied for comparison between baseline and peak of blood NGAL.

Results

Table 1. Subject characteristics according to baseline eGFR (ml/min/1.73m^2). Data are expressed as mean ± standard deviation (SD)

Baseline eGFR Range (ml/min/1.73m^2)	All (N=63) 15.7-83.8	15-30 (N=9) 15.7-26.9	30-45 (N=21) 30.7-44.0	45-60 (N=18) 49.8-59.2	60-90 (N=15) 62.2-83.8	p-value
Age	69.43 ± 9.32	69.00 ± 11.88	70.62 ± 9.98	68.11 ± 9.50	69.60 ± 6.88	0.873
Male	46 (73.0)	7 (77.8)	15 (71.4)	12 (66.7)	12 (80.0)	0.843
Female	17 (27.0)	2 (22.2)	6 (28.6)	6 (33.3)	3 (20.0)	0.843
White	54 (85.7)	6 (66.7)	19 (90.5)	15 (83.3)	14 (93.3)	0.128
Black	8 (12.7)	2 (22.2)	2 (9.5)	3 (16.7)	1 (6.7)	0.128
Other Race	1 (1.6)	1 (11.1)	0 (0)	0 (0)	0 (0)	-
Diabetes	22 (34.9)	7 (77.8)	5 (23.8)	7(38.9)	3 (20.0)	0.630
Atrial Fibrillation	7 (11.1)	3 (33.3)	4 (19.0)	0 (0)	0 (0)	-
Weight (kg)	155.21±65.93	185.33 ± 45.87	134.24 ± 61.95	134.83 ± 72.71	190.93 ± 54.80	0.014*
SBP (mmHg)	146.27±29.83	150.56 ± 31.84	158.38 ± 35.36	138.11 ± 17.20	136.53 ± 28.22	0.083
DBP (mmHg)	80.05±13.57	79.22 ± 18.70	82.00 ± 12.00	76.67 ± 12.99	81.87 ± 13.42	0.613
Cr (mg/dl)	1.54±0.49	2.40 ± 0.30	1.73 ± 0.28	1.30 ± 0.18	1.04 ± 0.17	0.0005*
BUN (mg/dl)	27.66±12.37	39.67 ± 15.68	31.97 ± 12.51	24.11 ± 7.07	18.67 ± 5.46	0.0003*
eGFR CKD EPI	48.17±16.45	26.36 ± 4.38	37.17 ± 4.81	53.07 ± 5.03	70.76 ± 7.68	0.0005*
Base NGAL(ng/ml)	191.32±141.92	360.29 ± 227.94	224.72 ± 117.43	132.29 ± 67.88	114.02 ± 57.42	0.0001*
Iso-osmolar contrast	28 (44.4)	9 (100.0)	10 (47.6)	5 (27.8)	4 (26.7)	0.001*
contrast volume (ml)	131.87±66.19	80.22 ± 39.69	126.71 ± 62.39	134.61 ± 65.07	166.80 ± 68.75	0.017*
Prophylactic NAC	30 (47.6)	8 (88.9)	14 (66.7)	5 (27.8)	3 (20.0)	0.0004*
Pre-procedure iv fluid (ml)	1074.56±770.76	973.00 ± 543.41	770.86 ± 777.47	1088.88 ± 714.61	1455.31 ± 826.19	0.137

*NOTE: eGFR: estimated Glomerular Filtration Rate; SBP:Systolic Blood Pressure; DBP:Diastolic Blood Pressure; Cr:creatinine; Base=baseline NGAL, *p<0.05*

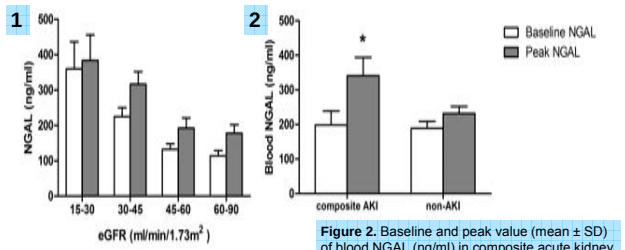

Figure 1. Baseline and peak value (mean ± SD) of blood NGAL (ng/ml) according to the range of eGFR (ml/min/1.73m^2)

Figure 2. Baseline and peak value (mean ± SD) of blood NGAL (ng/ml) in composite acute kidney injury group (combined KDIGO clinical and subclinical CI-AKI) and non-acute kidney injury group; ***p < 0.05***

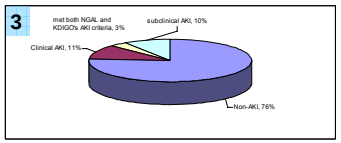

Figure 3. Pie chart of the clinical outcomes; no CI-AKI (n=48), subclinical CI-AKI (n=7), clinical KDIGO CI-AKI (n=8), with two subjects meeting both subclinical and clinical criteria.

Table 2 Independent traditional predictors for the outcome of composite subclinical or clinical CI-AKI after contrast exposure by binary logistic regression.

Independent variables	B	S.E.	Wald	Sig.	Exp (B)
(Constant)	- 2.577	1.137	5.135	0.023	0.076
eGFR CKD EPI	0.019	0.019	0.941	0.332	1.019
Diabetes	1.204	0.648	3.453	0.063	3.334

Discussion

❑ Doubling of blood NGAL detected nearly an entirely new and equal sized group of subjects who experienced a significant renal injury from iodinated contrast. Our findings suggest NGAL is a promising complementary marker to Cr in the detection of CI-AKI.

❑ In our previous analysis from ENCINO, we suggested that the baseline NGAL is crucial for interpretation of NGAL change in subjects with eGFR < 90 ml/min/1.73 m^2. Thus, use of a doubling of NGAL allows for a variable level of baseline NGAL concentration and could be proposed as a reasonable conceptual starting point to understand subclinical CI-AKI.

❑ The biologic response to toxic injury to the kidney mediated by contrast is dependent on the relative nephron mass reflected by the eGFR. In CKD, there is sustained up-regulation of NGAL production by viable distal renal tubular cells in an attempt to mitigate chronic oxidative stress catalyzed by intra- and extracellular poorly-liganded iron.

❑ Hemodialysis patients with residual renal function had significantly lower serum NGAL compared with those who were anuric. There are numerous sources of NGAL production e.g. cardiomyocytes, pneumocytes, prostate cells, and leukocytes. Thus, it is possible that intravascular iodinated contrast is triggering the production and release of NGAL into the blood from sites outside of and in addition to the kidney.

❑ We identified 8 patients who developed AKI according to 2012 KDIGO guidelines. The KDIGO definition allows for a longer detection window if a greater rise in serum Cr is detected or a sustained reduction in urine output is observed.

❑ The emerging concept of subclinical AKI manifested by a rise in NGAL or other marker of structural kidney damage, without a sufficient rise in serum Cr to meet conventional definition, has confirmed to be associated with an increase in morbidity and mortality.

❑ Our data suggest that blood NGAL could be used as a means to detect "subclinical CI-AKI" nearly doubling the case identification, and possibly expanding the possibilities for early prevention, treatment, and monitoring.

Limitation: Our study has all the limitations of small prospective studies. We recruited relatively few women and African American subjects. Thus, our data of NGAL cannot be considered representative for these groups. Peak blood NGAL appeared to occur at 48 hours post-catheterization, thus, additional measurements beyond this time frame would have been valuable. We lacked assessment of internal validity with respect to the degree of chronic and acute kidney disease assessed by other biomarkers e.g. kidney injury molecule-1, L-type fatty acid binding protein, interleukin-18, alpha/pi-glutathione S-transferase, or cystatin-C.

Conclusion

In summary, we characterized the baseline value of blood NGAL in various stages of CKD. In each stage, the post-procedure NGAL rose above the baseline level. Using NGAL in addition to KDIGO criteria identified larger numbers of patients considered to have a composite of subclinical and clinical CI-AKI. Future studies are needed using both novel markers for subclinical CI-AKI and serum Cr for conventional definitions of CI-AKI to evaluate the short and long-term risk of clinical outcomes including acceleration of the progression of CKD, rehospitalization, cardiac events, and mortality.

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