Plasma neutrophil gelatinase-associated lipocalin as an early diagnostic biomarker for acute kidney injury following cardiac surgery

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critical care medicine

by

Mohamed Ali Mohamed Badawy

M.B.B.CH,MASTER

Supervised by

Dr.Hisham Ali Elaasar,MD

Professor of critical care medicine

Cairo university

Dr.Gamal Hamed Ahmed,MD

Professor of critical care medicine

Cairo university

Dr.Hamdy Mohamed Saber,MD
Lecturer of critical care medicine

Beni-Sweif university

Dr.Inas Abdellatif Ahmed,MD
lecturer of biochemistry

Cairo university

Faculty of Medicine

Cairo University

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Abstract

***Introduction**: Acute kidney injury is well recognized for its impact on the outcome of patients admitted to the intensive care unit (ICU) and The extent of perioperative renal impairment ranges from subclinical injury to established renal failure requiring dialysis.*

The pursuit of improved biomarkers for the early diagnosis of AKI and its outcomes is an area of intense contemporary research, Recent studies have demonstrated the utility of early NGAL measurements for predicting clinical outcomes of AKI.

***Methodology** :our study was conducted on forty patients scheduled to have either on-pump or off-pump cardiac surgery during the period from February 2009 till June 2010, Spot plasma samples at (2 and 12 hours)intervals after cardiac surgery for measurement of plasma NGAL and serum creatinine) were obtained from all patients and RIFLE criteria were calculated at baseline and daily during the first five postoperative days taking in consideration Strict measures to avoid postoperative volume depletion and prerenal azotemia through using standard fluid regimen allowing all patients to receive at least 80%of their maintainance fluid requirements during the first 24 hours after surgery and 100% subsequently.*

***Results:** Exploring the diagnostic yield of NGAL levels in our study , the development of acute kidney injury in our studied population was highly and significantly correlated to 2HNGAL level with P value (0.0001)and a mean 2HNGAL of 310±65 in AKI patients compared to 140±51 in non-AKI patients , also it was significantly correlated to 12HNGAL level with P value (0.02) and a mean 12HNGAL of 210±103 in AKI patients compared to 147±53 in non-AKI patients.also, Upon attempting to find out the best cutoff limits of both 2HNGAL and 12HNGAL as diagnostic markers of AKI using ROC curve analysis , it had been discovered that the best cutoff value for 2HNGAL was **169ng/ml that yields a sensitivity of 100% and a specificity of 80%,** on the other hand , the best cutoff value for 12HNGAL was **130ng/ml that yields a sensitivity of 80% and a specificity of 55%** .*

***Conclusion:** NGAL measurement represents an early and reliable marker of AKI following cardiac surgery that could be in the future a therapeutic strategy modifying agent.*

***Key words :** ICU , NGAL , AKI , RIFLE.*

List of Abbreviations

12HNGAL	NGAL measured 12 hours after surgery
2HNGAL	NGAL measured 2 hours after surgery
ACEI	Angiotensin converting enzyme inhibitor
ADH	Anti-diuretic hormone
ADQI	Acute dialysis quality initiative
AF	Atrial fibrillation
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ANP	Atrial natriuretic peptide
APACHE	Acute physiology and chronic health evaluation
APCs	Antigen presenting cells
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
ARF-D	Acute renal failure requiring dialysis
ATN	Acute tubular necrosis
AUC	Area under curve
BUN	Blood urea nitrogen
CABG	Coronary artrey bypass grafting
CD	Cluster of differentiation
CKD	Chronic kidney disease
Cl	Chloride
COPD	Chronic obstructive pulmonary disease

CPB	Cardiopulmonary bypass
CVD	cerebrovuscular disease
DCs	Dendritic cells
DM	Diabetes mellitus
ECF	Extracellular fluid
ELISA	Enzyme linked immunosorbent assay
ESKD	End-stage kidney disease
FeNa	Fractional excretion of sodium
FeU	Fractional excretion of urea
GFR	Glomerular filteration rate
HCT	Haematocrit
HTN	Hypertension
IABP	Intraaortic ballon pump
ICAM	Intercellular adhesion molecules
ICU	Intensive care unit
IFN	Interferones
IL-18	Interleukin-18
IRI	Ischaemia-reperfusion injury
IVP	Intravenous pyelography
k	potassium
Kda	Kilo-dalton
KIM-1	Kidney injury molecule -1
Kpa	kilopascal
Lcn2	Lipocalin 2
LVEF	Left ventricular ejection fraction

m RNA	Messenger ribonucleic acid
m TAL	Thick ascending limb
MHC	Major histocompatibility
MI	Myocardial infarction
Na	Sodium
NAC	N-acetyl cysteine
NF-B	Nuclear factor kappa -B
NGAL	Neutrophil gelatinase associated lipocalin
NKT	Natural killer T cells
NSAIDS	Non-steroidal anti-inflammatory drugs
NYHA	Newyork heart association
PMN	Polymorph nuclear cells(neutrophils)
PRA	Prerenal azotemia
RCTs	Randomised controlled trials
RIFLE	**R**isk,**I**njury,**F**ailure,**L**oss,**E**ndstage
ROC	Receiver operating characteristics
RRT	Renal replacement therapy
SOFA	Sequential organ failure assessment
TECs	Tubular epithelial cells
TLRs	Toll-like receptors
UOP	Urine output

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Introduction

Acute kidney injury is well recognized for its impact on the outcome of patients admitted to the intensive care unit (ICU). Illness severity scores such as the Acute Physiology and Chronic Health Evaluation version III (APACHE III) scoring system [1] and the Sequential Organ Failure Assessment score (SOFA) [2] both weigh kidney dysfunction heavily (20% and 16.6% of the total scores for acute physiology).

When a subject presents with symptoms of angina pectoris, measurement of biomarkers such as troponin that are released from damaged myocytes can rapidly identify acute myocardial injury, allowing for timely interventions and a dramatic decrease in mortality. The analogous condition of the kidney, acute kidney injury (AKI), has been referred to as angina renalis, and the similarities end right there[1].

Renal dysfunction following cardiopulmonary bypass (CPB) is well recognized. The extent of perioperative renal impairment ranges from subclinical injury to established renal failure requiring dialysis. Its incidence varies considerably, depending on the definition and criteria used in the different studies.

Acute renal failure (ARF) affects 1-5% of patients and remains a major cause of morbidity and mortality. Co-morbidities, including diabetes mellitus, impaired left ventricular function and advanced age, are recognized predisposing factors. The pathophysiology is multifactorial and is thought related to the systemic inflammatory response and renal hypoperfusion secondary to extracorporeal circulation.

Non-pulsatile flow during CPB is thought to be an important aetiological factor, resulting in renal vasoconstriction and ischaemic renal injury[3].

A theoretical reduction in the incidence and severity of postoperative renal impairment has been proposed by advocating the use of pulsatile flow during CPB, or eliminating CPB, especially in high-risk patients. The current evidence, however, is conflicting[3].

AKI is largely asymptomatic, and establishing the diagnosis in the estimated 5% of hospitalized patients and a third of intensive care patients who suffer from the disease currently hinges on serial serum creatinine measurements. Unfortunately, creatinine is a notoriously delayed and unreliable indicator of AKI for a variety of reasons.first,more than 50% of renal function must be lost before detecting any s.creatinine change,second,s.creatinine doesnot depict renal function until a steady state has been reached which may require several days[4].

The pursuit of improved biomarkers for the early diagnosis of AKI and its outcomes is an area of intense contemporary research. For answers, we must turn to the kidney itself. Indeed, understanding the early stress response of the kidney to acute injuries has revealed a number of potential biomarkers.

Human NGAL was originally identified as a 25-kDa protein covalently bound to gelatinase from neutrophils . Like other lipocalins, NGAL forms a barrel-shaped tertiary structure with a hydrophobic calyx that binds small lipophilic molecules[5].

Recent studies have demonstrated the utility of early NGAL measurements for predicting clinical outcomes of AKI.

In children undergoing cardiac surgery, the 2-h post-operative plasma NGAL levels measured by Triage® Device strongly correlated with duration and severity of AKI, and length of hospital stay. In addition, the 12-h plasma NGAL strongly correlated with mortality[6].

Aim of the work

The aim of our study was:

- Proving that plasma neutrophil gelatinase-associated lipocalin is an earlier and more accurate biomarker rather than serum creatinine in predicting acute renal injury in post cardiac surgery patients.
- Finding any correlations between plasma NGAL levels and need for dialysis,ICU stay, renal impairement and overall mortality.

Chapter 1 :Acute kidney injury following cardiac surgery

A-Introduction

The field of acute nephrology has seen significant changes in recent times. These changes go to the core of many significant clinical issues. They affect the definition and classification of acute kidney dysfunction, our understanding of its epidemiology, our ability to make earlier diagnoses, our ability to use novel imaging modalities to understand its pathogenesis, and our insight into why acute kidney injury (AKI) might occur under different clinical circumstances including cardiac surgery, septic shock, radiocontrast agent exposure, liver disease and various toxins.

Advances in our understanding have affected our strategies for intervention which have been directed toward the modulation of inflammation, improvement in fluid therapy, administration of antioxidants, optimization of dialytic technique, and development of new dialytic paradigms with the introduction of bio-assist devices.

Finally, new pathophysiological insights have enabled us to better appreciate how to predict outcome in these patients as well as understand the significance of renal recovery and the factors that modulate it[7].

This term has been proposed and accepted because it deals with the full spectrum of the syndrome of kidney involvement in a variety of acute diseases and emphasizes that even minor changes in renal function which may be dismissed clinically carry an independent association with an increased risk of mortality[8-9] .

Using this conceptual framework, new definitions and classifications have been developed and one, the RIFLE classification, has now been studied and found robust in 1 250,000 patients.

Armed with a definition and a classification system and with the understanding that even minor subclinical injury to the kidney may matter, what should be emphasized is the need to develop early biomarkers of such injury [10] and appreciate the role of inflammation [11] in inducing injury. Through sufficiently early diagnosis, a better classification system and a clearer understanding of the pathogenesis, these steps promise, for the first time in a long while, to deliver novel and effective therapies for patients.

Clinicians need to keep abreast of these evolutions if they wish to continue to deliver the best care to their patients[11].

B-Definition &classification

(1)Acute organ distress

The presence of, or risk for, acute dysfunction of vital organs defined as the presence of altered organ function in acutely ill patients such that homeostasis cannot be maintained without intervention is a defining aspect of critical illness. Indeed, the purpose of critical care is to provide life-sustaining organ support (e.g. mechanical ventilation) and to rapidly intervene to save organ function (e.g. opening of coronary arteries).

For most vital organs, injury and reduced function are tightly correlated. For some organs injury can be severe before decreased function is apparent – for example as much as 80% of the liver can be damaged before clinical symptoms are manifest.

For other organs dysfunction may be greater than what is produced by irreversible injury (e.g. stunned or hibernating myocardium).However, the kidney may be unique in that the earliest clinical manifestations of injury are also consistent with ‘perfect’ function.